An Overview of Blood
By the end of this section, you will be able to:

- Identify the primary functions of blood in transportation, defense, and maintenance of homeostasis
- Name the fluid component of blood and the three major types of formed elements, and identify their relative proportions in a blood sample
- Discuss the unique physical characteristics of blood
- Identify the composition of blood plasma, including its most important solutes and plasma proteins

Recall that **blood** is a connective tissue. Like all connective tissues, it is made up of cellular elements and an extracellular matrix. The cellular elements—referred to as the **formed elements**—include **red blood cells (RBCs)**, **white blood cells (WBCs)**, and cell fragments called **platelets**. The extracellular matrix, called **plasma**, makes blood unique among connective tissues because it is fluid. This fluid, which is mostly water, perpetually suspends the formed elements and enables them to circulate throughout the body within the cardiovascular system.

Functions of Blood

The primary function of blood is to deliver oxygen and nutrients to and remove wastes from body cells, but that is only the beginning of the story. The specific functions of blood also include defense, distribution of heat, and maintenance of homeostasis.

Transportation

Nutrients from the foods you eat are absorbed in the digestive tract. Most of these travel in the bloodstream directly to the liver, where they are processed and released back into the bloodstream for delivery to body cells. Oxygen from the air you breathe diffuses into the blood, which moves from the lungs to the heart, which then pumps it out to the rest of the body. Moreover, endocrine glands scattered throughout the body release their

products, called hormones, into the bloodstream, which carries them to distant target cells. Blood also picks up cellular wastes and byproducts, and transports them to various organs for removal. For instance, blood moves carbon dioxide to the lungs for exhalation from the body, and various waste products are transported to the kidneys and liver for excretion from the body in the form of urine or bile.

Defense

Many types of WBCs protect the body from external threats, such as disease-causing bacteria that have entered the bloodstream in a wound. Other WBCs seek out and destroy internal threats, such as cells with mutated DNA that could multiply to become cancerous, or body cells infected with viruses.

When damage to the vessels results in bleeding, blood platelets and certain proteins dissolved in the plasma, the fluid portion of the blood, interact to block the ruptured areas of the blood vessels involved. This protects the body from further blood loss.

Maintenance of Homeostasis

Recall that body temperature is regulated via a classic negative-feedback loop. If you were exercising on a warm day, your rising core body temperature would trigger several homeostatic mechanisms, including increased transport of blood from your core to your body periphery, which is typically cooler. As blood passes through the vessels of the skin, heat would be dissipated to the environment, and the blood returning to your body core would be cooler. In contrast, on a cold day, blood is diverted away from the skin to maintain a warmer body core. In extreme cases, this may result in frostbite.

Blood also helps to maintain the chemical balance of the body. Proteins and other compounds in blood act as buffers, which thereby help to regulate the

pH of body tissues. Blood also helps to regulate the water content of body cells.

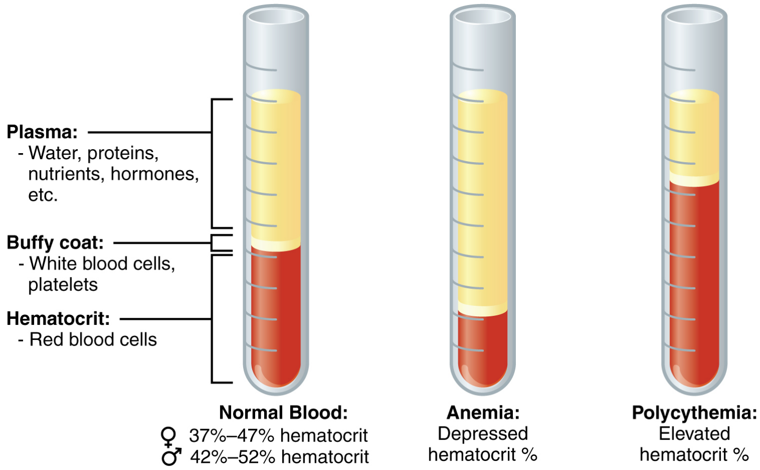
Composition of Blood

You have probably had blood drawn from a superficial vein in your arm, which was then sent to a lab for analysis. Some of the most common blood tests—for instance, those measuring lipid or glucose levels in plasma—determine which substances are present within blood and in what quantities. Other blood tests check for the composition of the blood itself, including the quantities and types of formed elements.

One such test, called a **hematocrit**, measures the percentage of RBCs, clinically known as erythrocytes, in a blood sample. It is performed by spinning the blood sample in a specialized centrifuge, a process that causes the heavier elements suspended within the blood sample to separate from the lightweight, liquid plasma ([link]). Because the heaviest elements in blood are the erythrocytes, these settle at the very bottom of the hematocrit tube. Located above the erythrocytes is a pale, thin layer composed of the remaining formed elements of blood. These are the WBCs, clinically known as leukocytes, and the platelets, cell fragments also called thrombocytes. This layer is referred to as the **buffy coat** because of its color; it normally constitutes less than 1 percent of a blood sample. Above the buffy coat is the blood plasma, normally a pale, straw-colored fluid, which constitutes the remainder of the sample.

The volume of erythrocytes after centrifugation is also commonly referred to as **packed cell volume (PCV)**. In normal blood, about 45 percent of a sample is erythrocytes. The hematocrit of any one sample can vary significantly, however, about 36–50 percent, according to gender and other factors. Normal hematocrit values for females range from 37 to 47, with a mean value of 41; for males, hematocrit ranges from 42 to 52, with a mean of 47. The percentage of other formed elements, the WBCs and platelets, is extremely small so it is not normally considered with the hematocrit. So the mean plasma percentage is the percent of blood that is not erythrocytes: for females, it is approximately 59 (or 100 minus 41), and for males, it is approximately 53 (or 100 minus 47).

Composition of Blood



The cellular elements of blood include a vast number of erythrocytes and comparatively fewer leukocytes and platelets. Plasma is the fluid in which the formed elements are suspended. A sample of blood spun in a centrifuge reveals that plasma is the lightest component. It floats at the top of the tube separated from the heaviest elements, the erythrocytes, by a buffy coat of leukocytes and platelets. Hematocrit is the percentage of the total sample that is comprised of erythrocytes. Depressed and elevated hematocrit levels are shown for comparison.

Characteristics of Blood

When you think about blood, the first characteristic that probably comes to mind is its color. Blood that has just taken up oxygen in the lungs is bright red, and blood that has released oxygen in the tissues is a more dusky red. This is because hemoglobin is a pigment that changes color, depending upon the degree of oxygen saturation.

Blood is viscous and somewhat sticky to the touch. It has a viscosity approximately five times greater than water. Viscosity is a measure of a fluid's thickness or resistance to flow, and is influenced by the presence of the plasma proteins and formed elements within the blood. The viscosity of blood has a dramatic impact on blood pressure and flow. Consider the difference in flow between water and honey. The more viscous honey would demonstrate a greater resistance to flow than the less viscous water. The same principle applies to blood.

The normal temperature of blood is slightly higher than normal body temperature—about 38 °C (or 100.4 °F), compared to 37 °C (or 98.6 °F) for an internal body temperature reading, although daily variations of 0.5 °C are normal. Although the surface of blood vessels is relatively smooth, as blood flows through them, it experiences some friction and resistance, especially as vessels age and lose their elasticity, thereby producing heat. This accounts for its slightly higher temperature.

The pH of blood averages about 7.4; however, it can range from 7.35 to 7.45 in a healthy person. Blood is therefore somewhat more basic (alkaline) on a chemical scale than pure water, which has a pH of 7.0. Blood contains numerous buffers that actually help to regulate pH.

Blood constitutes approximately 8 percent of adult body weight. Adult males typically average about 5 to 6 liters of blood. Females average 4–5 liters.

Blood Plasma

Like other fluids in the body, plasma is composed primarily of water: In fact, it is about 92 percent water. Dissolved or suspended within this water is a mixture of substances, most of which are proteins. There are literally hundreds of substances dissolved or suspended in the plasma, although many of them are found only in very small quantities.

Note:

Visit this site for a list of normal levels established for many of the substances found in a sample of blood. Serum, one of the specimen types included, refers to a sample of plasma after clotting factors have been removed. What types of measurements are given for levels of glucose in the blood?

Plasma Proteins

About 7 percent of the volume of plasma—nearly all that is not water—is made of proteins. These include several plasma proteins (proteins that are unique to the plasma), plus a much smaller number of regulatory proteins, including enzymes and some hormones. The major components of plasma are summarized in [link].

The three major groups of plasma proteins are as follows:

- **Albumin** is the most abundant of the plasma proteins. Manufactured by the liver, albumin molecules serve as binding proteins—transport vehicles for fatty acids and steroid hormones. Recall that lipids are hydrophobic; however, their binding to albumin enables their transport in the watery plasma. Albumin is also the most significant contributor to the osmotic pressure of blood; that is, its presence holds water inside the blood vessels and draws water from the tissues, across blood vessel walls, and into the bloodstream. This in turn helps to maintain both blood volume and blood pressure. Albumin normally accounts for approximately 54 percent of the total plasma protein content, in clinical levels of 3.5–5.0 g/dL blood.
- The second most common plasma proteins are the **globulins**. A heterogeneous group, there are three main subgroups known as alpha, beta, and gamma globulins. The alpha and beta globulins transport

iron, lipids, and the fat-soluble vitamins A, D, E, and K to the cells; like albumin, they also contribute to osmotic pressure. The gamma globulins are proteins involved in immunity and are better known as an **antibodies** or **immunoglobulins**. Although other plasma proteins are produced by the liver, immunoglobulins are produced by specialized leukocytes known as plasma cells. (Seek additional content for more information about immunoglobulins.) Globulins make up approximately 38 percent of the total plasma protein volume, in clinical levels of 1.0–1.5 g/dL blood.

- The least abundant plasma protein is **fibrinogen**. Like albumin and the alpha and beta globulins, fibrinogen is produced by the liver. It is essential for blood clotting, a process described later in this chapter. Fibrinogen accounts for about 7 percent of the total plasma protein volume, in clinical levels of 0.2–0.45 g/dL blood.

Other Plasma Solutes

In addition to proteins, plasma contains a wide variety of other substances. These include various electrolytes, such as sodium, potassium, and calcium ions; dissolved gases, such as oxygen, carbon dioxide, and nitrogen; various organic nutrients, such as vitamins, lipids, glucose, and amino acids; and metabolic wastes. All of these nonprotein solutes combined contribute approximately 1 percent to the total volume of plasma.
Major Blood Components

Component and % of blood	Subcomponent and % of component	Type and % (where appropriate)	Site of production	Major function(s)
Plasma 46–63 percent	Water 92 percent	Fluid	Absorbed by intestinal tract or produced by metabolism	Transport medium
	Plasma proteins 7 percent	Albumin 54–60 percent	Liver	Maintain osmotic concentration, transport lipid molecules
		Globulins 35–38 percent	Alpha globulins—liver	Transport, maintain osmotic concentration
			Beta globulins—liver	Transport, maintain osmotic concentration
			Gamma globulins (immunoglobulins)—plasma cells	Immune responses
		Fibrinogen 4–7 percent	Liver	Blood clotting in hemostasis
	Regulatory proteins <1 percent	Hormones and enzymes	Various sources	Regulate various body functions
	Other solutes 1 percent	Nutrients, gases, and wastes	Absorbed by intestinal tract, exchanged in respiratory system, or produced by cells	Numerous and varied
Formed elements 37–54 percent	Erythrocytes 99 percent	Erythrocytes	Red bone marrow	Transport gases, primarily oxygen and some carbon dioxide
	Leukocytes <1 percent Platelets <1 percent	Granular leukocytes: neutrophils eosinophils basophils	Red bone marrow	Nonspecific immunity
		Agranular leukocytes: lymphocytes monocytes	Lymphocytes: bone marrow and lymphatic tissue	Lymphocytes: specific immunity
			Monocytes: red bone marrow	Monocytes: nonspecific immunity
	Platelets <1 percent		Megakaryocytes: red bone marrow	Hemostasis

Note:
Career Connection
Phlebotomy and Medical Lab Technology
Phlebotomists are professionals trained to draw blood (phleb- = “a blood vessel”; -tomy = “to cut”). When more than a few drops of blood are

required, phlebotomists perform a venipuncture, typically of a surface vein in the arm. They perform a capillary stick on a finger, an earlobe, or the heel of an infant when only a small quantity of blood is required. An arterial stick is collected from an artery and used to analyze blood gases. After collection, the blood may be analyzed by medical laboratories or perhaps used for transfusions, donations, or research. While many allied health professionals practice phlebotomy, the American Society of Phlebotomy Technicians issues certificates to individuals passing a national examination, and some large labs and hospitals hire individuals expressly for their skill in phlebotomy.

Medical or clinical laboratories employ a variety of individuals in technical positions:

- Medical technologists (MT), also known as clinical laboratory technologists (CLT), typically hold a bachelor’s degree and certification from an accredited training program. They perform a wide variety of tests on various body fluids, including blood. The information they provide is essential to the primary care providers in determining a diagnosis and in monitoring the course of a disease and response to treatment.
- Medical laboratory technicians (MLT) typically have an associate’s degree but may perform duties similar to those of an MT.
- Medical laboratory assistants (MLA) spend the majority of their time processing samples and carrying out routine assignments within the lab. Clinical training is required, but a degree may not be essential to obtaining a position.

Chapter Review

Blood is a fluid connective tissue critical to the transportation of nutrients, gases, and wastes throughout the body; to defend the body against infection and other threats; and to the homeostatic regulation of pH, temperature, and other internal conditions. Blood is composed of formed elements—erythrocytes, leukocytes, and cell fragments called platelets—and a fluid extracellular matrix called plasma. More than 90 percent of plasma is water.

The remainder is mostly plasma proteins—mainly albumin, globulins, and fibrinogen—and other dissolved solutes such as glucose, lipids, electrolytes, and dissolved gases. Because of the formed elements and the plasma proteins and other solutes, blood is sticky and more viscous than water. It is also slightly alkaline, and its temperature is slightly higher than normal body temperature.

Interactive Link Questions

Exercise:

Problem:

Visit this site for a list of normal levels established for many of the substances found in a sample of blood. Serum, one of the specimen types included, refers to a sample of plasma after clotting factors have been removed. What types of measurements are given for levels of glucose in the blood?

Solution:

There are values given for percent saturation, tension, and blood gas, and there are listings for different types of hemoglobin.

Review Questions

Exercise:

Problem: Which of the following statements about blood is true?

a. Blood is about 92 percent water.
b. Blood is slightly more acidic than water.
c. Blood is slightly more viscous than water.
d. Blood is slightly more salty than seawater.

Solution:

C

Exercise:

Problem: Which of the following statements about albumin is true?

a. It draws water out of the blood vessels and into the body’s tissues.
b. It is the most abundant plasma protein.
c. It is produced by specialized leukocytes called plasma cells.
d. All of the above are true.

Solution:

B

Exercise:

Problem:

Which of the following plasma proteins is *not* produced by the liver?

a. fibrinogen
b. alpha globulin
c. beta globulin
d. immunoglobulin

Solution:

D

Critical Thinking Questions

Exercise:

Problem:

A patient’s hematocrit is 42 percent. Approximately what percentage of the patient’s blood is plasma?

Solution:

The patient’s blood is approximately 58 percent plasma (since the buffy coat is less than 1 percent).

Exercise:

Problem:

Why would it be incorrect to refer to the formed elements as cells?

Solution:

The formed elements include erythrocytes and leukocytes, which are cells (although mature erythrocytes do not have a nucleus); however, the formed elements also include platelets, which are not true cells but cell fragments.

Exercise:

Problem:

True or false: The buffy coat is the portion of a blood sample that is made up of its proteins.

Solution:

False. The buffy coat is the portion of blood that is made up of its leukocytes and platelets.

Glossary

albumin

most abundant plasma protein, accounting for most of the osmotic pressure of plasma

antibodies
: (also, immunoglobulins or gamma globulins) antigen-specific proteins produced by specialized B lymphocytes that protect the body by binding to foreign objects such as bacteria and viruses

blood
: liquid connective tissue composed of formed elements—erythrocytes, leukocytes, and platelets—and a fluid extracellular matrix called plasma; component of the cardiovascular system

buffy coat
: thin, pale layer of leukocytes and platelets that separates the erythrocytes from the plasma in a sample of centrifuged blood

fibrinogen
: plasma protein produced in the liver and involved in blood clotting

formed elements
: cellular components of blood; that is, erythrocytes, leukocytes, and platelets

globulins
: heterogeneous group of plasma proteins that includes transport proteins, clotting factors, immune proteins, and others

hematocrit
: (also, packed cell volume) volume percentage of erythrocytes in a sample of centrifuged blood

immunoglobulins
: (also, antibodies or gamma globulins) antigen-specific proteins produced by specialized B lymphocytes that protect the body by binding to foreign objects such as bacteria and viruses

packed cell volume (PCV)

(also, hematocrit) volume percentage of erythrocytes present in a sample of centrifuged blood

plasma
: in blood, the liquid extracellular matrix composed mostly of water that circulates the formed elements and dissolved materials throughout the cardiovascular system

platelets
: (also, thrombocytes) one of the formed elements of blood that consists of cell fragments broken off from megakaryocytes

red blood cells (RBCs)
: (also, erythrocytes) one of the formed elements of blood that transports oxygen

white blood cells (WBCs)
: (also, leukocytes) one of the formed elements of blood that provides defense against disease agents and foreign materials

Production of the Formed Elements
By the end of this section, you will be able to:

- Trace the generation of the formed elements of blood from bone marrow stem cells
- Discuss the role of hemopoietic growth factors in promoting the production of the formed elements

The lifespan of the formed elements is very brief. Although one type of leukocyte called memory cells can survive for years, most erythrocytes, leukocytes, and platelets normally live only a few hours to a few weeks. Thus, the body must form new blood cells and platelets quickly and continuously. When you donate a unit of blood during a blood drive (approximately 475 mL, or about 1 pint), your body typically replaces the donated plasma within 24 hours, but it takes about 4 to 6 weeks to replace the blood cells. This restricts the frequency with which donors can contribute their blood. The process by which this replacement occurs is called **hemopoiesis**, or hematopoiesis (from the Greek root haima- = “blood”; -poiesis = “production”).

Sites of Hemopoiesis

Prior to birth, hemopoiesis occurs in a number of tissues, beginning with the yolk sac of the developing embryo, and continuing in the fetal liver, spleen, lymphatic tissue, and eventually the red bone marrow. Following birth, most hemopoiesis occurs in the red marrow, a connective tissue within the spaces of spongy (cancellous) bone tissue. In children, hemopoiesis can occur in the medullary cavity of long bones; in adults, the process is largely restricted to the cranial and pelvic bones, the vertebrae, the sternum, and the proximal epiphyses of the femur and humerus.

Throughout adulthood, the liver and spleen maintain their ability to generate the formed elements. This process is referred to as extramedullary hemopoiesis (meaning hemopoiesis outside the medullary cavity of adult bones). When a disease such as bone cancer destroys the bone marrow, causing hemopoiesis to fail, extramedullary hemopoiesis may be initiated.

Differentiation of Formed Elements from Stem Cells

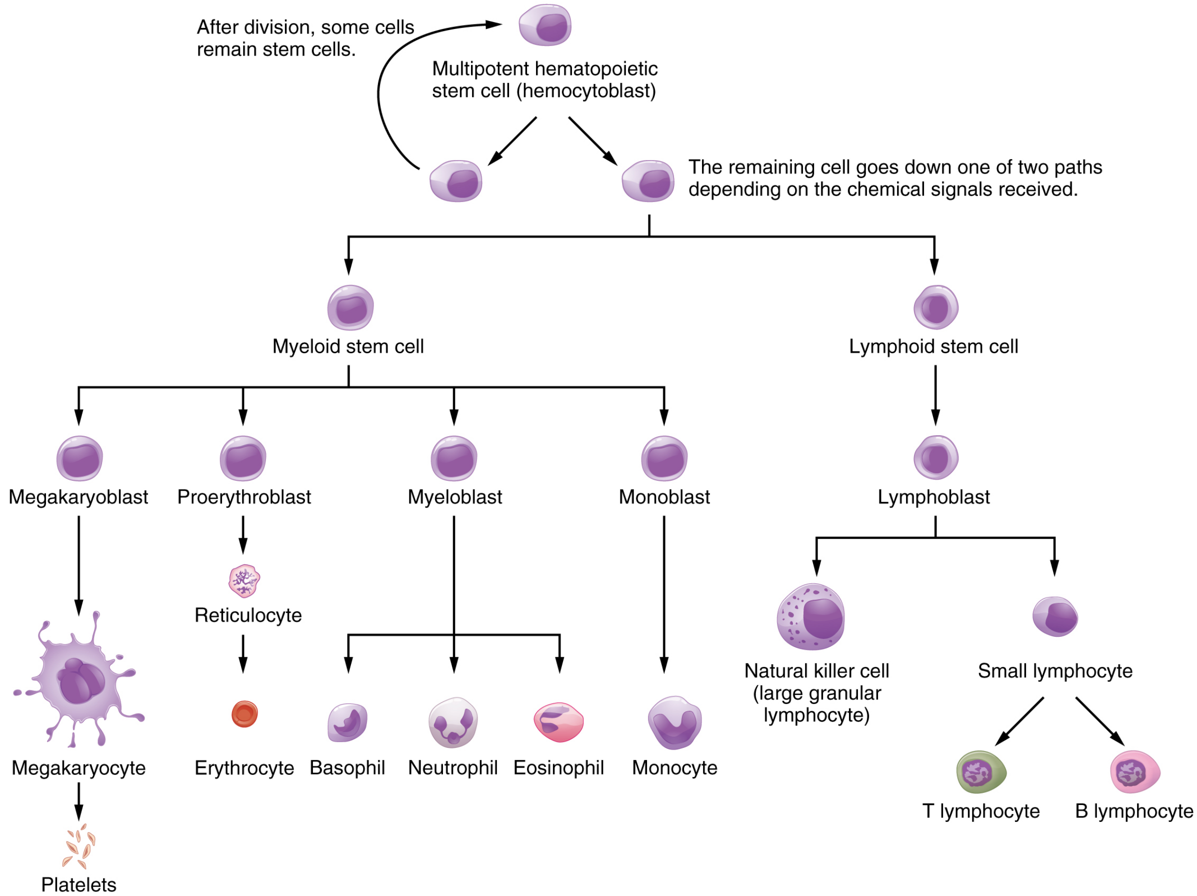
All formed elements arise from stem cells of the red bone marrow. Recall that stem cells undergo mitosis plus cytokinesis (cellular division) to give rise to new daughter cells: One of these remains a stem cell and the other differentiates into one of any number of diverse cell types. Stem cells may be viewed as occupying a hierarchal system, with some loss of the ability to diversify at each step. The **totipotent stem cell** is the zygote, or fertilized egg. The totipotent (toti- = "all") stem cell gives rise to all cells of the human body. The next level is the **pluripotent stem cell**, which gives rise to multiple types of cells of the body and some of the supporting fetal membranes. Beneath this level, the mesenchymal cell is a stem cell that develops only into types of connective tissue, including fibrous connective tissue, bone, cartilage, and blood, but not epithelium, muscle, and nervous tissue. One step lower on the hierarchy of stem cells is the **hemopoietic stem cell**, or **hemocytoblast**. All of the formed elements of blood originate from this specific type of cell.

Hemopoiesis begins when the hemopoietic stem cell is exposed to appropriate chemical stimuli collectively called **hemopoietic growth factors**, which prompt it to divide and differentiate. One daughter cell remains a hemopoietic stem cell, allowing hemopoiesis to continue. The other daughter cell becomes either of two types of more specialized stem cells ([link]):

- **Lymphoid stem cells** give rise to a class of leukocytes known as lymphocytes, which include the various T cells, B cells, and natural killer (NK) cells, all of which function in immunity. However, hemopoiesis of lymphocytes progresses somewhat differently from the process for the other formed elements. In brief, lymphoid stem cells quickly migrate from the bone marrow to lymphatic tissues, including the lymph nodes, spleen, and thymus, where their production and differentiation continues. B cells are so named since they mature in the bone marrow, while T cells mature in the thymus.
- **Myeloid stem cells** give rise to all the other formed elements, including the erythrocytes; megakaryocytes that produce platelets; and

a myeloblast lineage that gives rise to monocytes and three forms of granular leukocytes: neutrophils, eosinophils, and basophils.

Hematopoietic System of Bone Marrow



Hemopoiesis is the proliferation and differentiation of the formed elements of blood.

Lymphoid and myeloid stem cells do not immediately divide and differentiate into mature formed elements. As you can see in [link], there are several intermediate stages of precursor cells (literally, forerunner cells), many of which can be recognized by their names, which have the suffix -blast. For instance, megakaryoblasts are the precursors of megakaryocytes, and proerythroblasts become reticulocytes, which eject their nucleus and most other organelles before maturing into erythrocytes.

Hemopoietic Growth Factors

Development from stem cells to precursor cells to mature cells is again initiated by hemopoietic growth factors. These include the following:

- **Erythropoietin (EPO)** is a glycoprotein hormone secreted by the interstitial fibroblast cells of the kidneys in response to low oxygen levels. It prompts the production of erythrocytes. Some athletes use synthetic EPO as a performance-enhancing drug (called blood doping) to increase RBC counts and subsequently increase oxygen delivery to tissues throughout the body. EPO is a banned substance in most organized sports, but it is also used medically in the treatment of certain anemia, specifically those triggered by certain types of cancer, and other disorders in which increased erythrocyte counts and oxygen levels are desirable.
- **Thrombopoietin**, another glycoprotein hormone, is produced by the liver and kidneys. It triggers the development of megakaryocytes into platelets.
- **Cytokines** are glycoproteins secreted by a wide variety of cells, including red bone marrow, leukocytes, macrophages, fibroblasts, and endothelial cells. They act locally as autocrine or paracrine factors, stimulating the proliferation of progenitor cells and helping to stimulate both nonspecific and specific resistance to disease. There are two major subtypes of cytokines known as colony-stimulating factors and interleukins.

    - **Colony-stimulating factors (CSFs)** are glycoproteins that act locally, as autocrine or paracrine factors. Some trigger the differentiation of myeloblasts into granular leukocytes, namely, neutrophils, eosinophils, and basophils. These are referred to as granulocyte CSFs. A different CSF induces the production of monocytes, called monocyte CSFs. Both granulocytes and monocytes are stimulated by GM-CSF; granulocytes, monocytes, platelets, and erythrocytes are stimulated by multi-CSF. Synthetic forms of these hormones are often administered to patients with various forms of cancer who are receiving chemotherapy to revive their WBC counts.

- **Interleukins** are another class of cytokine signaling molecules important in hemopoiesis. They were initially thought to be secreted uniquely by leukocytes and to communicate only with other leukocytes, and were named accordingly, but are now known to be produced by a variety of cells including bone marrow and endothelium. Researchers now suspect that interleukins may play other roles in body functioning, including differentiation and maturation of cells, producing immunity and inflammation. To date, more than a dozen interleukins have been identified, with others likely to follow. They are generally numbered IL-1, IL-2, IL-3, etc.

Note:
Everyday Connection
Blood Doping
In its original intent, the term blood doping was used to describe the practice of injecting by transfusion supplemental RBCs into an individual, typically to enhance performance in a sport. Additional RBCs would deliver more oxygen to the tissues, providing extra aerobic capacity, clinically referred to as VO_2 max. The source of the cells was either from the recipient (autologous) or from a donor with compatible blood (homologous). This practice was aided by the well-developed techniques of harvesting, concentrating, and freezing of the RBCs that could be later thawed and injected, yet still retain their functionality. These practices are considered illegal in virtually all sports and run the risk of infection, significantly increasing the viscosity of the blood and the potential for transmission of blood-borne pathogens if the blood was collected from another individual.
With the development of synthetic EPO in the 1980s, it became possible to provide additional RBCs by artificially stimulating RBC production in the bone marrow. Originally developed to treat patients suffering from anemia, renal failure, or cancer treatment, large quantities of EPO can be generated by recombinant DNA technology. Synthetic EPO is injected under the skin and can increase hematocrit for many weeks. It may also induce polycythemia and raise hematocrit to 70 or greater. This increased

viscosity raises the resistance of the blood and forces the heart to pump more powerfully; in extreme cases, it has resulted in death. Other drugs such as cobalt II chloride have been shown to increase natural EPO gene expression. Blood doping has become problematic in many sports, especially cycling. Lance Armstrong, winner of seven Tour de France and many other cycling titles, was stripped of his victories and admitted to blood doping in 2013.

Note:

Watch this video to see doctors discuss the dangers of blood doping in sports. What are the some potential side effects of blood doping?

Bone Marrow Sampling and Transplants

Sometimes, a healthcare provider will order a **bone marrow biopsy**, a diagnostic test of a sample of red bone marrow, or a **bone marrow transplant**, a treatment in which a donor’s healthy bone marrow—and its stem cells—replaces the faulty bone marrow of a patient. These tests and procedures are often used to assist in the diagnosis and treatment of various severe forms of anemia, such as thalassemia major and sickle cell anemia, as well as some types of cancer, specifically leukemia.

In the past, when a bone marrow sample or transplant was necessary, the procedure would have required inserting a large-bore needle into the region near the iliac crest of the pelvic bones (os coxae). This location was preferred, since its location close to the body surface makes it more

accessible, and it is relatively isolated from most vital organs. Unfortunately, the procedure is quite painful.

Now, direct sampling of bone marrow can often be avoided. In many cases, stem cells can be isolated in just a few hours from a sample of a patient's blood. The isolated stem cells are then grown in culture using the appropriate hemopoietic growth factors, and analyzed or sometimes frozen for later use.

For an individual requiring a transplant, a matching donor is essential to prevent the immune system from destroying the donor cells—a phenomenon known as tissue rejection. To treat patients with bone marrow transplants, it is first necessary to destroy the patient's own diseased marrow through radiation and/or chemotherapy. Donor bone marrow stem cells are then intravenously infused. From the bloodstream, they establish themselves in the recipient's bone marrow.

Chapter Review

Through the process of hemopoiesis, the formed elements of blood are continually produced, replacing the relatively short-lived erythrocytes, leukocytes, and platelets. Hemopoiesis begins in the red bone marrow, with hemopoietic stem cells that differentiate into myeloid and lymphoid lineages. Myeloid stem cells give rise to most of the formed elements. Lymphoid stem cells give rise only to the various lymphocytes designated as B and T cells, and NK cells. Hemopoietic growth factors, including erythropoietin, thrombopoietin, colony-stimulating factors, and interleukins, promote the proliferation and differentiation of formed elements.

Interactive Link Questions

Exercise:

Problem:

Watch this video to see doctors discuss the dangers of blood doping in sports. What are the some potential side effects of blood doping?

Solution:

Side effects can include heart disease, stroke, pulmonary embolism, and virus transmission.

Review Questions

Exercise:

Problem:

Which of the formed elements arise from myeloid stem cells?

a. B cells
b. natural killer cells
c. platelets
d. all of the above

Solution:

C

Exercise:

Problem:

Which of the following statements about erythropoietin is true?

a. It facilitates the proliferation and differentiation of the erythrocyte lineage.
b. It is a hormone produced by the thyroid gland.
c. It is a hemopoietic growth factor that prompts lymphoid stem cells to leave the bone marrow.
d. Both a and b are true.

Solution:

A

Exercise:

Problem:

Interleukins are associated primarily with which of the following?

a. production of various lymphocytes
b. immune responses
c. inflammation
d. all of the above

Solution:

D

Critical Thinking Questions

Exercise:

Problem:

Myelofibrosis is a disorder in which inflammation and scar tissue formation in the bone marrow impair hemopoiesis. One sign is an enlarged spleen. Why?

Solution:

When disease impairs the ability of the bone marrow to participate in hemopoiesis, extramedullary hemopoiesis begins in the patient’s liver and spleen. This causes the spleen to enlarge.

Exercise:

Problem:

Would you expect a patient with a form of cancer called acute myelogenous leukemia to experience impaired production of erythrocytes, or impaired production of lymphocytes? Explain your choice.

Solution:

The adjective myelogenous suggests a condition originating from (generated by) myeloid cells. Acute myelogenous leukemia impairs the production of erythrocytes and other mature formed elements of the myeloid stem cell lineage. Lymphocytes arise from the lymphoid stem cell line.

Glossary

bone marrow biopsy
: diagnostic test of a sample of red bone marrow

bone marrow transplant
: treatment in which a donor’s healthy bone marrow with its stem cells replaces diseased or damaged bone marrow of a patient

colony-stimulating factors (CSFs)
: glycoproteins that trigger the proliferation and differentiation of myeloblasts into granular leukocytes (basophils, neutrophils, and eosinophils)

cytokines
: class of proteins that act as autocrine or paracrine signaling molecules; in the cardiovascular system, they stimulate the proliferation of progenitor cells and help to stimulate both nonspecific and specific resistance to disease

erythropoietin (EPO)

glycoprotein that triggers the bone marrow to produce RBCs; secreted by the kidney in response to low oxygen levels

hemocytoblast
: hemopoietic stem cell that gives rise to the formed elements of blood

hemopoiesis
: production of the formed elements of blood

hemopoietic growth factors
: chemical signals including erythropoietin, thrombopoietin, colony-stimulating factors, and interleukins that regulate the differentiation and proliferation of particular blood progenitor cells

hemopoietic stem cell
: type of pluripotent stem cell that gives rise to the formed elements of blood (hemocytoblast)

interleukins
: signaling molecules that may function in hemopoiesis, inflammation, and specific immune responses

lymphoid stem cells
: type of hemopoietic stem cells that gives rise to lymphocytes, including various T cells, B cells, and NK cells, all of which function in immunity

myeloid stem cells
: type of hemopoietic stem cell that gives rise to some formed elements, including erythrocytes, megakaryocytes that produce platelets, and a myeloblast lineage that gives rise to monocytes and three forms of granular leukocytes (neutrophils, eosinophils, and basophils)

pluripotent stem cell
: stem cell that derives from totipotent stem cells and is capable of differentiating into many, but not all, cell types

totipotent stem cell

embryonic stem cell that is capable of differentiating into any and all cells of the body; enabling the full development of an organism

thrombopoietin

hormone secreted by the liver and kidneys that prompts the development of megakaryocytes into thrombocytes (platelets)

Erythrocytes

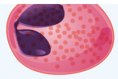
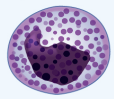
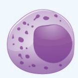
By the end of this section, you will be able to:

- Describe the anatomy of erythrocytes
- Discuss the various steps in the lifecycle of an erythrocyte
- Explain the composition and function of hemoglobin

The **erythrocyte**, commonly known as a red blood cell (or RBC), is by far the most common formed element: A single drop of blood contains millions of erythrocytes and just thousands of leukocytes. Specifically, males have about 5.4 million erythrocytes per microliter (μL) of blood, and females have approximately 4.8 million per μL. In fact, erythrocytes are estimated to make up about 25 percent of the total cells in the body. As you can imagine, they are quite small cells, with a mean diameter of only about 7–8 micrometers (μm) ([link]). The primary functions of erythrocytes are to pick up inhaled oxygen from the lungs and transport it to the body's tissues, and to pick up some (about 24 percent) carbon dioxide waste at the tissues and transport it to the lungs for exhalation. Erythrocytes remain within the vascular network. Although leukocytes typically leave the blood vessels to perform their defensive functions, movement of erythrocytes from the blood vessels is abnormal.

Summary of Formed Elements in Blood

Formed element	Major subtypes	Numbers present per microliter (μL) and mean (range)	Appearance in a standard blood smear	Summary of functions	Comments
Erythrocytes (red blood cells) 		5.2 million (4.4–6.0 million)	Flattened biconcave disk; no nucleus; pale red color	Transport oxygen and some carbon dioxide between tissues and lungs	Lifespan of approximately 120 days
Leukocytes (white blood cells)		7000 (5000–10,000)	Obvious dark-staining nucleus	All function in body defenses	Exit capillaries and move into tissues; lifespan of usually a few hours or days
	Granulocytes including neutrophils, eosinophils, and basophils	4360 (1800–9950)	Abundant granules in cytoplasm; nucleus normally lobed	Nonspecific (innate) resistance to disease	Classified according to membrane-bound granules in cytoplasm
	Neutrophils 	4150 (1800–7300)	Nuclear lobes increase with age; pale lilac granules	Phagocytic; particularly effective against bacteria. Release cytotoxic chemicals from granules	Most common leukocyte; lifespan of minutes to days
	Eosinophils 	165 (0–700)	Nucleus generally two-lobed; bright red-orange granules	Phagocytic cells; particularly effective with antigen- antibody	Lifespan of minutes to days

				complexes. Release antihistamines. Increase in allergies and parasitic infections	
	Basophils 	44 (0–150)	Nucleus generally two-lobed but difficult to see due to presence of heavy, dense, dark purple granules	Promotes inflammation	Least common leukocyte; lifespan unknown
	Agranulocytes including lymphocytes and monocytes	2640 (1700–4950)	Lack abundant granules in cytoplasm; have a simple-shaped nucleus that may be indented	Body defenses	Group consists of two major cell types from different lineages
	Lymphocytes  	2185 (1500–4000)	Spherical cells with a single often large nucleus occupying much of the cell's volume; stains purple; seen in large (natural killer cells) and small (B and T cells) variants	Primarily specific (adaptive) immunity: T cells directly attack other cells (cellular immunity); B cells release antibodies (humoral immunity); natural killer cells are similar to T cells but nonspecific	Initial cells originate in bone marrow, but secondary production occurs in lymphatic tissue; several distinct subtypes; memory cells form after exposure to a pathogen and rapidly increase responses to subsequent exposure; lifespan of many years
	Monocytes 	455 (200–950)	Largest leukocyte with an indented or horseshoe-shaped nucleus	Very effective phagocytic cells engulfing pathogens or worn out cells; also serve as antigen-presenting cells (APCs) for other components of the immune system	Produced in red bone marrow; referred to as macrophages after leaving circulation
Platelets 		350,000 (150,000–500,000)	Cellular fragments surrounded by a plasma membrane and containing granules; purple stain	Hemostasis plus release growth factors for repair and healing of tissue	Formed from megakaryocytes that remain in the red bone marrow and shed platelets into circulation

Shape and Structure of Erythrocytes

As an erythrocyte matures in the red bone marrow, it extrudes its nucleus and most of its other organelles. During the first day or two that it is in the circulation, an immature erythrocyte, known as a **reticulocyte**, will still typically contain remnants of organelles. Reticulocytes should comprise approximately 1–2 percent of the erythrocyte count and provide a rough estimate of the rate of RBC production, with abnormally low or high rates indicating deviations in the production of these cells. These remnants, primarily of networks (reticulum) of ribosomes, are quickly shed, however, and mature, circulating erythrocytes have few internal cellular structural components. Lacking mitochondria, for example, they rely on anaerobic respiration. This means that they do not utilize any of the oxygen they are transporting, so they can deliver it all to the tissues. They also lack

endoplasmic reticula and do not synthesize proteins. Erythrocytes do, however, contain some structural proteins that help the blood cells maintain their unique structure and enable them to change their shape to squeeze through capillaries. This includes the protein spectrin, a cytoskeletal protein element.

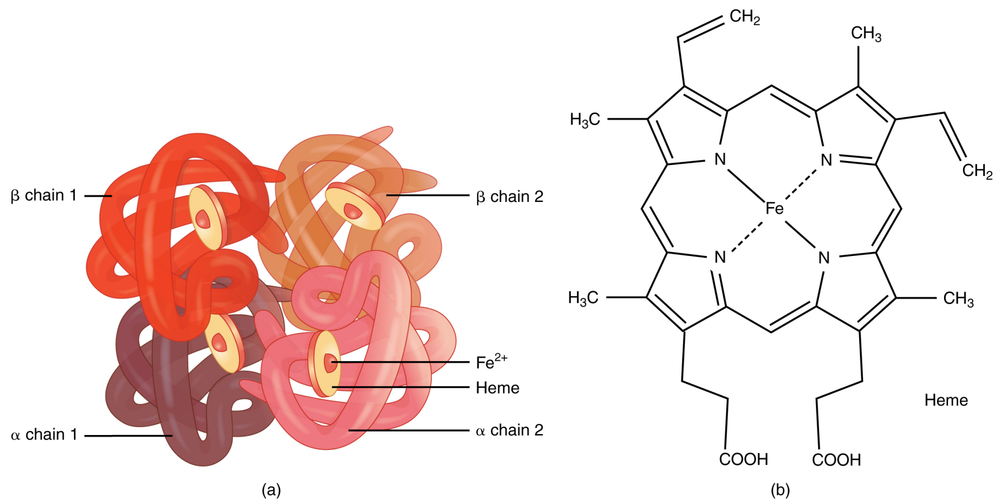
Erythrocytes are biconcave disks; that is, they are plump at their periphery and very thin in the center ([link]). Since they lack most organelles, there is more interior space for the presence of the hemoglobin molecules that, as you will see shortly, transport gases. The biconcave shape also provides a greater surface area across which gas exchange can occur, relative to its volume; a sphere of a similar diameter would have a lower surface area-to-volume ratio. In the capillaries, the oxygen carried by the erythrocytes can diffuse into the plasma and then through the capillary walls to reach the cells, whereas some of the carbon dioxide produced by the cells as a waste product diffuses into the capillaries to be picked up by the erythrocytes. Capillary beds are extremely narrow, slowing the passage of the erythrocytes and providing an extended opportunity for gas exchange to occur. However, the space within capillaries can be so minute that, despite their own small size, erythrocytes may have to fold in on themselves if they are to make their way through. Fortunately, their structural proteins like spectrin are flexible, allowing them to bend over themselves to a surprising degree, then spring back again when they enter a wider vessel. In wider vessels, erythrocytes may stack up much like a roll of coins, forming a rouleaux, from the French word for “roll.”

Shape of Red Blood Cells

Erythrocytes are biconcave discs with very shallow centers. This shape optimizes the ratio of surface area to volume, facilitating gas exchange. It also enables them to fold up as they move through narrow blood vessels.

Hemoglobin

Hemoglobin is a large molecule made up of proteins and iron. It consists of four folded chains of a protein called **globin**, designated alpha 1 and 2, and beta 1 and 2 ([link]**a**). Each of these globin molecules is bound to a red pigment molecule called **heme**, which contains an ion of iron (Fe^{2+}) ([link]**b**).
Hemoglobin



(a) A molecule of hemoglobin contains four globin proteins, each of which is bound to one molecule of the iron-containing pigment heme. (b) A single erythrocyte can contain 300 million hemoglobin molecules, and thus more than 1 billion oxygen molecules.

Each iron ion in the heme can bind to one oxygen molecule; therefore, each hemoglobin molecule can transport four oxygen molecules. An individual erythrocyte may contain about 300 million hemoglobin molecules, and therefore can bind to and transport up to 1.2 billion oxygen molecules (see [link]**b**).

In the lungs, hemoglobin picks up oxygen, which binds to the iron ions, forming **oxyhemoglobin**. The bright red, oxygenated hemoglobin travels to the body tissues, where it releases some of the oxygen molecules, becoming darker red **deoxyhemoglobin**, sometimes referred to as reduced hemoglobin. Oxygen release depends on the need for oxygen in the surrounding tissues, so hemoglobin rarely if ever leaves all of its oxygen behind. In the capillaries, carbon dioxide enters the bloodstream. About 76 percent dissolves in the plasma, some of it remaining as dissolved CO_2, and the remainder forming bicarbonate ion. About 23–24 percent of it binds to the amino acids in hemoglobin, forming a molecule known as **carbaminohemoglobin**. From the capillaries, the hemoglobin carries

carbon dioxide back to the lungs, where it releases it for exchange of oxygen.

Changes in the levels of RBCs can have significant effects on the body's ability to effectively deliver oxygen to the tissues. Ineffective hematopoiesis results in insufficient numbers of RBCs and results in one of several forms of anemia. An overproduction of RBCs produces a condition called polycythemia. The primary drawback with polycythemia is not a failure to directly deliver enough oxygen to the tissues, but rather the increased viscosity of the blood, which makes it more difficult for the heart to circulate the blood.

In patients with insufficient hemoglobin, the tissues may not receive sufficient oxygen, resulting in another form of anemia. In determining oxygenation of tissues, the value of greatest interest in healthcare is the percent saturation; that is, the percentage of hemoglobin sites occupied by oxygen in a patient's blood. Clinically this value is commonly referred to simply as "percent sat."

Percent saturation is normally monitored using a device known as a pulse oximeter, which is applied to a thin part of the body, typically the tip of the patient's finger. The device works by sending two different wavelengths of light (one red, the other infrared) through the finger and measuring the light with a photodetector as it exits. Hemoglobin absorbs light differentially depending upon its saturation with oxygen. The machine calibrates the amount of light received by the photodetector against the amount absorbed by the partially oxygenated hemoglobin and presents the data as percent saturation. Normal pulse oximeter readings range from 95–100 percent. Lower percentages reflect **hypoxemia**, or low blood oxygen. The term hypoxia is more generic and simply refers to low oxygen levels. Oxygen levels are also directly monitored from free oxygen in the plasma typically following an arterial stick. When this method is applied, the amount of oxygen present is expressed in terms of partial pressure of oxygen or simply pO_2 and is typically recorded in units of millimeters of mercury, mm Hg.

The kidneys filter about 180 liters (~380 pints) of blood in an average adult each day, or about 20 percent of the total resting volume, and thus serve as ideal sites for receptors that determine oxygen saturation. In response to

hypoxemia, less oxygen will exit the vessels supplying the kidney, resulting in hypoxia (low oxygen concentration) in the tissue fluid of the kidney where oxygen concentration is actually monitored. Interstitial fibroblasts within the kidney secrete EPO, thereby increasing erythrocyte production and restoring oxygen levels. In a classic negative-feedback loop, as oxygen saturation rises, EPO secretion falls, and vice versa, thereby maintaining homeostasis. Populations dwelling at high elevations, with inherently lower levels of oxygen in the atmosphere, naturally maintain a hematocrit higher than people living at sea level. Consequently, people traveling to high elevations may experience symptoms of hypoxemia, such as fatigue, headache, and shortness of breath, for a few days after their arrival. In response to the hypoxemia, the kidneys secrete EPO to step up the production of erythrocytes until homeostasis is achieved once again. To avoid the symptoms of hypoxemia, or altitude sickness, mountain climbers typically rest for several days to a week or more at a series of camps situated at increasing elevations to allow EPO levels and, consequently, erythrocyte counts to rise. When climbing the tallest peaks, such as Mt. Everest and K2 in the Himalayas, many mountain climbers rely upon bottled oxygen as they near the summit.

Lifecycle of Erythrocytes

Production of erythrocytes in the marrow occurs at the staggering rate of more than 2 million cells per second. For this production to occur, a number of raw materials must be present in adequate amounts. These include the same nutrients that are essential to the production and maintenance of any cell, such as glucose, lipids, and amino acids. However, erythrocyte production also requires several trace elements:

- Iron. We have said that each heme group in a hemoglobin molecule contains an ion of the trace mineral iron. On average, less than 20 percent of the iron we consume is absorbed. Heme iron, from animal foods such as meat, poultry, and fish, is absorbed more efficiently than non-heme iron from plant foods. Upon absorption, iron becomes part of the body's total iron pool. The bone marrow, liver, and spleen can store iron in the protein compounds **ferritin** and **hemosiderin**. Ferroportin transports the iron across the intestinal cell plasma

membranes and from its storage sites into tissue fluid where it enters the blood. When EPO stimulates the production of erythrocytes, iron is released from storage, bound to transferrin, and carried to the red marrow where it attaches to erythrocyte precursors.

- Copper. A trace mineral, copper is a component of two plasma proteins, hephaestin and ceruloplasmin. Without these, hemoglobin could not be adequately produced. Located in intestinal villi, hephaestin enables iron to be absorbed by intestinal cells. Ceruloplasmin transports copper. Both enable the oxidation of iron from Fe^{2+} to Fe^{3+}, a form in which it can be bound to its transport protein, **transferrin**, for transport to body cells. In a state of copper deficiency, the transport of iron for heme synthesis decreases, and iron can accumulate in tissues, where it can eventually lead to organ damage.
- Zinc. The trace mineral zinc functions as a co-enzyme that facilitates the synthesis of the heme portion of hemoglobin.
- B vitamins. The B vitamins folate and vitamin B_{12} function as co-enzymes that facilitate DNA synthesis. Thus, both are critical for the synthesis of new cells, including erythrocytes.

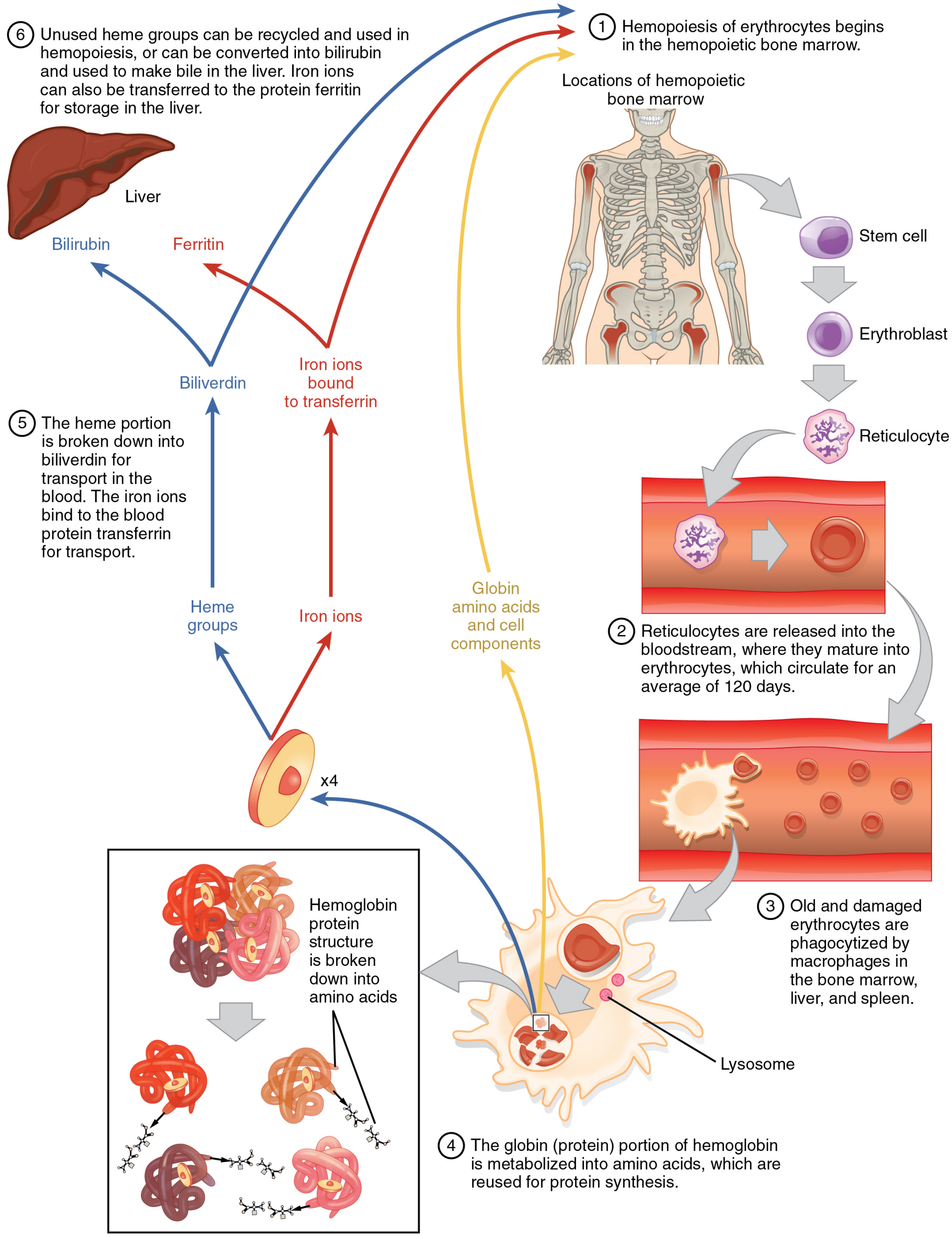
Erythrocytes live up to 120 days in the circulation, after which the worn-out cells are removed by a type of myeloid phagocytic cell called a **macrophage**, located primarily within the bone marrow, liver, and spleen. The components of the degraded erythrocytes' hemoglobin are further processed as follows:

- Globin, the protein portion of hemoglobin, is broken down into amino acids, which can be sent back to the bone marrow to be used in the production of new erythrocytes. Hemoglobin that is not phagocytized is broken down in the circulation, releasing alpha and beta chains that are removed from circulation by the kidneys.
- The iron contained in the heme portion of hemoglobin may be stored in the liver or spleen, primarily in the form of ferritin or hemosiderin, or carried through the bloodstream by transferrin to the red bone marrow for recycling into new erythrocytes.
- The non-iron portion of heme is degraded into the waste product **biliverdin**, a green pigment, and then into another waste product,

bilirubin, a yellow pigment. Bilirubin binds to albumin and travels in the blood to the liver, which uses it in the manufacture of bile, a compound released into the intestines to help emulsify dietary fats. In the large intestine, bacteria breaks the bilirubin apart from the bile and converts it to urobilinogen and then into stercobilin. It is then eliminated from the body in the feces. Broad-spectrum antibiotics typically eliminate these bacteria as well and may alter the color of feces. The kidneys also remove any circulating bilirubin and other related metabolic byproducts such as urobilins and secrete them into the urine.

The breakdown pigments formed from the destruction of hemoglobin can be seen in a variety of situations. At the site of an injury, biliverdin from damaged RBCs produces some of the dramatic colors associated with bruising. With a failing liver, bilirubin cannot be removed effectively from circulation and causes the body to assume a yellowish tinge associated with jaundice. Stercobilins within the feces produce the typical brown color associated with this waste. And the yellow of urine is associated with the urobilins.

The erythrocyte lifecycle is summarized in [link].
Erythrocyte Lifecycle



Erythrocytes are produced in the bone marrow and sent into the circulation. At the end of their lifecycle, they are destroyed by

macrophages, and their components are recycled.

Disorders of Erythrocytes

The size, shape, and number of erythrocytes, and the number of hemoglobin molecules can have a major impact on a person’s health. When the number of RBCs or hemoglobin is deficient, the general condition is called **anemia**. There are more than 400 types of anemia and more than 3.5 million Americans suffer from this condition. Anemia can be broken down into three major groups: those caused by blood loss, those caused by faulty or decreased RBC production, and those caused by excessive destruction of RBCs. Clinicians often use two groupings in diagnosis: The kinetic approach focuses on evaluating the production, destruction, and removal of RBCs, whereas the morphological approach examines the RBCs themselves, paying particular emphasis to their size. A common test is the mean corpuscle volume (MCV), which measures size. Normal-sized cells are referred to as normocytic, smaller-than-normal cells are referred to as microcytic, and larger-than-normal cells are referred to as macrocytic. Reticulocyte counts are also important and may reveal inadequate production of RBCs. The effects of the various anemias are widespread, because reduced numbers of RBCs or hemoglobin will result in lower levels of oxygen being delivered to body tissues. Since oxygen is required for tissue functioning, anemia produces fatigue, lethargy, and an increased risk for infection. An oxygen deficit in the brain impairs the ability to think clearly, and may prompt headaches and irritability. Lack of oxygen leaves the patient short of breath, even as the heart and lungs work harder in response to the deficit.

Blood loss anemias are fairly straightforward. In addition to bleeding from wounds or other lesions, these forms of anemia may be due to ulcers, hemorrhoids, inflammation of the stomach (gastritis), and some cancers of the gastrointestinal tract. The excessive use of aspirin or other nonsteroidal anti-inflammatory drugs such as ibuprofen can trigger ulceration and gastritis. Excessive menstruation and loss of blood during childbirth are also potential causes.

Anemias caused by faulty or decreased RBC production include sickle cell anemia, iron deficiency anemia, vitamin deficiency anemia, and diseases of the bone marrow and stem cells.

- A characteristic change in the shape of erythrocytes is seen in **sickle cell disease** (also referred to as sickle cell anemia). A genetic disorder, it is caused by production of an abnormal type of hemoglobin, called hemoglobin S, which delivers less oxygen to tissues and causes erythrocytes to assume a sickle (or crescent) shape, especially at low oxygen concentrations ([link]). These abnormally shaped cells can then become lodged in narrow capillaries because they are unable to fold in on themselves to squeeze through, blocking blood flow to tissues and causing a variety of serious problems from painful joints to delayed growth and even blindness and cerebrovascular accidents (strokes). Sickle cell anemia is a genetic condition particularly found in individuals of African descent.

Sickle Cells

Sickle cell anemia is caused by a mutation in one of the hemoglobin genes. Erythrocytes produce an abnormal type of

hemoglobin, which causes the cell to take on a sickle or crescent shape. (credit: Janice Haney Carr)

- Iron deficiency anemia is the most common type and results when the amount of available iron is insufficient to allow production of sufficient heme. This condition can occur in individuals with a deficiency of iron in the diet and is especially common in teens and children as well as in vegans and vegetarians. Additionally, iron deficiency anemia may be caused by either an inability to absorb and transport iron or slow, chronic bleeding.
- Vitamin-deficient anemias generally involve insufficient vitamin B12 and folate.
    - Megaloblastic anemia involves a deficiency of vitamin B12 and/or folate, and often involves diets deficient in these essential nutrients. Lack of meat or a viable alternate source, and overcooking or eating insufficient amounts of vegetables may lead to a lack of folate.
    - Pernicious anemia is caused by poor absorption of vitamin B12 and is often seen in patients with Crohn’s disease (a severe intestinal disorder often treated by surgery), surgical removal of the intestines or stomach (common in some weight loss surgeries), intestinal parasites, and AIDS.
    - Pregnancies, some medications, excessive alcohol consumption, and some diseases such as celiac disease are also associated with vitamin deficiencies. It is essential to provide sufficient folic acid during the early stages of pregnancy to reduce the risk of neurological defects, including spina bifida, a failure of the neural tube to close.
- Assorted disease processes can also interfere with the production and formation of RBCs and hemoglobin. If myeloid stem cells are

defective or replaced by cancer cells, there will be insufficient quantities of RBCs produced.

  - Aplastic anemia is the condition in which there are deficient numbers of RBC stem cells. Aplastic anemia is often inherited, or it may be triggered by radiation, medication, chemotherapy, or infection.
  - **Thalassemia** is an inherited condition typically occurring in individuals from the Middle East, the Mediterranean, African, and Southeast Asia, in which maturation of the RBCs does not proceed normally. The most severe form is called Cooley's anemia.
  - Lead exposure from industrial sources or even dust from paint chips of iron-containing paints or pottery that has not been properly glazed may also lead to destruction of the red marrow.

- Various disease processes also can lead to anemias. These include chronic kidney diseases often associated with a decreased production of EPO, hypothyroidism, some forms of cancer, lupus, and rheumatoid arthritis.

In contrast to anemia, an elevated RBC count is called **polycythemia** and is detected in a patient's elevated hematocrit. It can occur transiently in a person who is dehydrated; when water intake is inadequate or water losses are excessive, the plasma volume falls. As a result, the hematocrit rises. For reasons mentioned earlier, a mild form of polycythemia is chronic but normal in people living at high altitudes. Some elite athletes train at high elevations specifically to induce this phenomenon. Finally, a type of bone marrow disease called polycythemia vera (from the Greek vera = "true") causes an excessive production of immature erythrocytes. Polycythemia vera can dangerously elevate the viscosity of blood, raising blood pressure and making it more difficult for the heart to pump blood throughout the body. It is a relatively rare disease that occurs more often in men than women, and is more likely to be present in elderly patients those over 60 years of age.

Chapter Review

The most abundant formed elements in blood, erythrocytes are red, biconcave disks packed with an oxygen-carrying compound called hemoglobin. The hemoglobin molecule contains four globin proteins bound to a pigment molecule called heme, which contains an ion of iron. In the bloodstream, iron picks up oxygen in the lungs and drops it off in the tissues; the amino acids in hemoglobin then transport carbon dioxide from the tissues back to the lungs. Erythrocytes live only 120 days on average, and thus must be continually replaced. Worn-out erythrocytes are phagocytized by macrophages and their hemoglobin is broken down. The breakdown products are recycled or removed as wastes: Globin is broken down into amino acids for synthesis of new proteins; iron is stored in the liver or spleen or used by the bone marrow for production of new erythrocytes; and the remnants of heme are converted into bilirubin, or other waste products that are taken up by the liver and excreted in the bile or removed by the kidneys. Anemia is a deficiency of RBCs or hemoglobin, whereas polycythemia is an excess of RBCs.

Review Questions

Exercise:

Problem:

Which of the following statements about mature, circulating erythrocytes is true?

a. They have no nucleus.
b. They are packed with mitochondria.
c. They survive for an average of 4 days.
d. All of the above

Solution:

A

Exercise:

Problem:A molecule of hemoglobin ________.

a. is shaped like a biconcave disk packed almost entirely with iron
b. contains four glycoprotein units studded with oxygen
c. consists of four globin proteins, each bound to a molecule of heme
d. can carry up to 120 molecules of oxygen

Solution:

C

Exercise:

Problem:

The production of healthy erythrocytes depends upon the availability of ________.

a. copper
b. zinc
c. vitamin B_{12}
d. copper, zinc, and vitamin B_{12}

Solution:

D

Exercise:

Problem:

Aging and damaged erythrocytes are removed from the circulation by ________.

a. myeoblasts
b. monocytes

c. macrophages
d. mast cells

Solution:

C

Exercise:

Problem:

A patient has been suffering for 2 months with a chronic, watery diarrhea. A blood test is likely to reveal ________.

a. a hematocrit below 30 percent
b. hypoxemia
c. anemia
d. polycythemia

Solution:

D

Critical Thinking Questions

Exercise:

Problem:

A young woman has been experiencing unusually heavy menstrual bleeding for several years. She follows a strict vegan diet (no animal foods). She is at risk for what disorder, and why?

Solution:

She is at risk for anemia, because her unusually heavy menstrual bleeding results in excessive loss of erythrocytes each month. At the

same time, her vegan diet means that she does not have dietary sources of heme iron. The non-heme iron she consumes in plant foods is not as well absorbed as heme iron.

Exercise:

Problem:

A patient has thalassemia, a genetic disorder characterized by abnormal synthesis of globin proteins and excessive destruction of erythrocytes. This patient is jaundiced and is found to have an excessive level of bilirubin in his blood. Explain the connection.

Solution:

Bilirubin is a breakdown product of the non-iron component of heme, which is cleaved from globin when erythrocytes are degraded. Excessive erythrocyte destruction would deposit excessive bilirubin in the blood. Bilirubin is a yellowish pigment, and high blood levels can manifest as yellowed skin.

Glossary

anemia
: deficiency of red blood cells or hemoglobin

bilirubin
: yellowish bile pigment produced when iron is removed from heme and is further broken down into waste products

biliverdin
: green bile pigment produced when the non-iron portion of heme is degraded into a waste product; converted to bilirubin in the liver

carbaminohemoglobin
: compound of carbon dioxide and hemoglobin, and one of the ways in which carbon dioxide is carried in the blood

deoxyhemoglobin
molecule of hemoglobin without an oxygen molecule bound to it

erythrocyte
(also, red blood cell) mature myeloid blood cell that is composed mostly of hemoglobin and functions primarily in the transportation of oxygen and carbon dioxide

ferritin
protein-containing storage form of iron found in the bone marrow, liver, and spleen

globin
heme-containing globular protein that is a constituent of hemoglobin

heme
red, iron-containing pigment to which oxygen binds in hemoglobin

hemoglobin
oxygen-carrying compound in erythrocytes

hemosiderin
protein-containing storage form of iron found in the bone marrow, liver, and spleen

hypoxemia
below-normal level of oxygen saturation of blood (typically <95 percent)

macrophage
phagocytic cell of the myeloid lineage; a matured monocyte

oxyhemoglobin
molecule of hemoglobin to which oxygen is bound

polycythemia
elevated level of hemoglobin, whether adaptive or pathological

reticulocyte

immature erythrocyte that may still contain fragments of organelles

sickle cell disease
(also, sickle cell anemia) inherited blood disorder in which hemoglobin molecules are malformed, leading to the breakdown of RBCs that take on a characteristic sickle shape

thalassemia
inherited blood disorder in which maturation of RBCs does not proceed normally, leading to abnormal formation of hemoglobin and the destruction of RBCs

transferrin
plasma protein that binds reversibly to iron and distributes it throughout the body

Leukocytes and Platelets
By the end of this section, you will be able to:

- Describe the general characteristics of leukocytes
- Classify leukocytes according to their lineage, their main structural features, and their primary functions
- Discuss the most common malignancies involving leukocytes
- Identify the lineage, basic structure, and function of platelets

The **leukocyte**, commonly known as a white blood cell (or WBC), is a major component of the body's defenses against disease. Leukocytes protect the body against invading microorganisms and body cells with mutated DNA, and they clean up debris. Platelets are essential for the repair of blood vessels when damage to them has occurred; they also provide growth factors for healing and repair. See [link] for a summary of leukocytes and platelets.

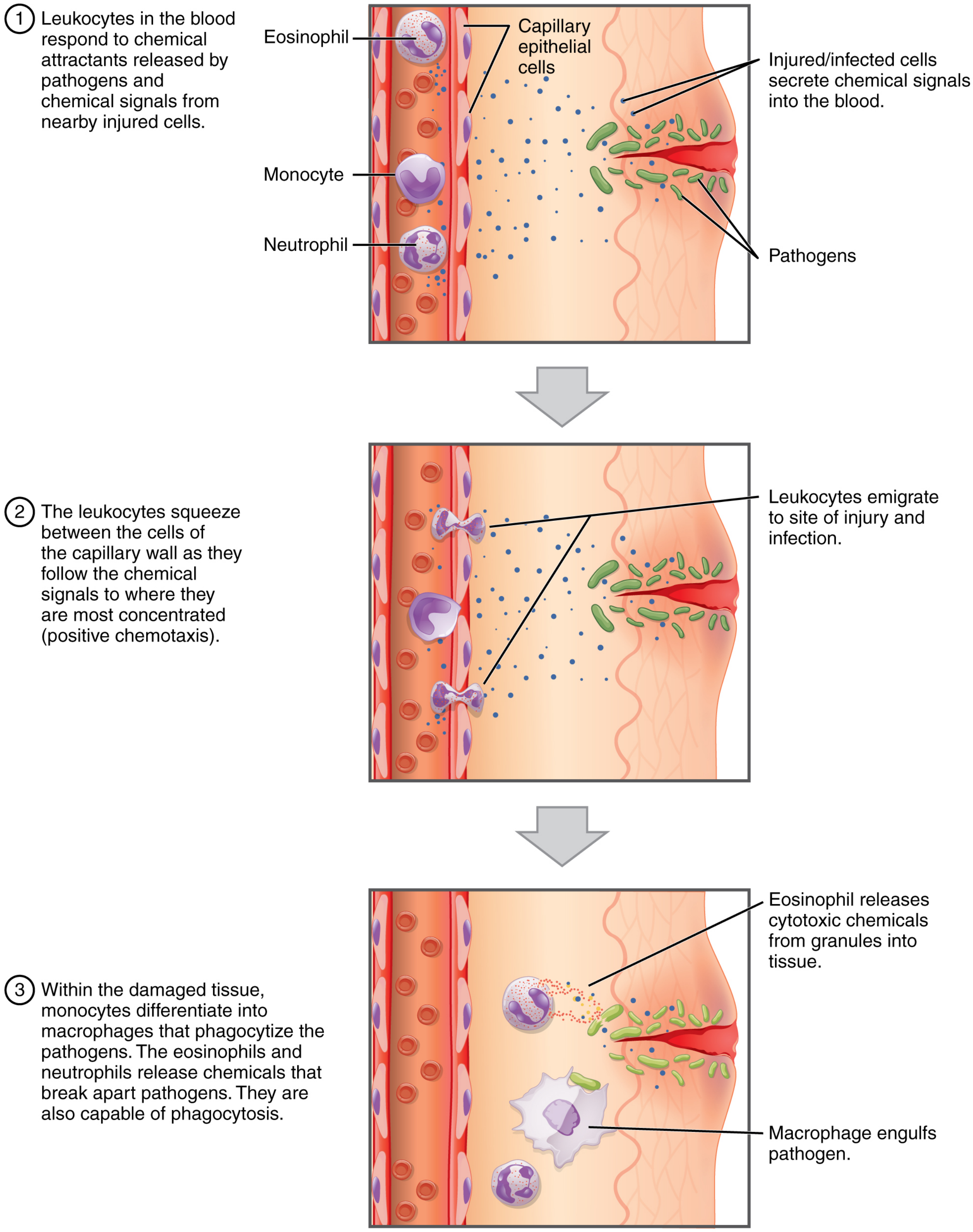
Characteristics of Leukocytes

Although leukocytes and erythrocytes both originate from hematopoietic stem cells in the bone marrow, they are very different from each other in many significant ways. For instance, leukocytes are far less numerous than erythrocytes: Typically there are only 5000 to 10,000 per μL. They are also larger than erythrocytes and are the only formed elements that are complete cells, possessing a nucleus and organelles. And although there is just one type of erythrocyte, there are many types of leukocytes. Most of these types have a much shorter lifespan than that of erythrocytes, some as short as a few hours or even a few minutes in the case of acute infection.

One of the most distinctive characteristics of leukocytes is their movement. Whereas erythrocytes spend their days circulating within the blood vessels, leukocytes routinely leave the bloodstream to perform their defensive functions in the body's tissues. For leukocytes, the vascular network is simply a highway they travel and soon exit to reach their true destination. When they arrive, they are often given distinct names, such as macrophage or microglia, depending on their function. As shown in [link], they leave the capillaries—the smallest blood vessels—or other small vessels through a

process known as **emigration** (from the Latin for “removal”) or **diapedesis** (dia- = “through”; -pedan = “to leap”) in which they squeeze through adjacent cells in a blood vessel wall.

Once they have exited the capillaries, some leukocytes will take up fixed positions in lymphatic tissue, bone marrow, the spleen, the thymus, or other organs. Others will move about through the tissue spaces very much like amoebas, continuously extending their plasma membranes, sometimes wandering freely, and sometimes moving toward the direction in which they are drawn by chemical signals. This attracting of leukocytes occurs because of **positive chemotaxis** (literally “movement in response to chemicals”), a phenomenon in which injured or infected cells and nearby leukocytes emit the equivalent of a chemical “911” call, attracting more leukocytes to the site. In clinical medicine, the differential counts of the types and percentages of leukocytes present are often key indicators in making a diagnosis and selecting a treatment.
Emigration



Leukocytes exit the blood vessel and then move through the connective tissue of the dermis toward the site of a wound. Some leukocytes, such as the eosinophil and neutrophil, are characterized

as granular leukocytes. They release chemicals from their granules that destroy pathogens; they are also capable of phagocytosis. The monocyte, an agranular leukocyte, differentiates into a macrophage that then phagocytizes the pathogens.

Classification of Leukocytes

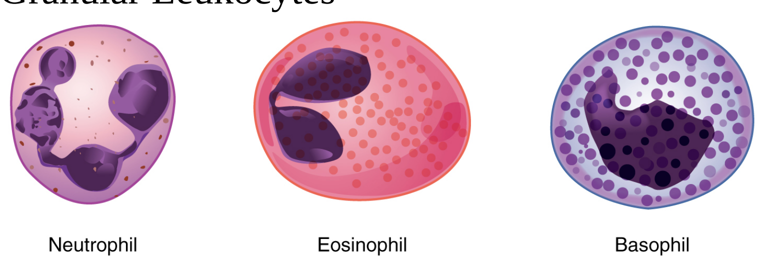
When scientists first began to observe stained blood slides, it quickly became evident that leukocytes could be divided into two groups, according to whether their cytoplasm contained highly visible granules:

- **Granular leukocytes** contain abundant granules within the cytoplasm. They include neutrophils, eosinophils, and basophils (you can view their lineage from myeloid stem cells in [link]).
- While granules are not totally lacking in **agranular leukocytes**, they are far fewer and less obvious. Agranular leukocytes include monocytes, which mature into macrophages that are phagocytic, and lymphocytes, which arise from the lymphoid stem cell line.

Granular Leukocytes

We will consider the granular leukocytes in order from most common to least common. All of these are produced in the red bone marrow and have a short lifespan of hours to days. They typically have a lobed nucleus and are classified according to which type of stain best highlights their granules ([link]).

Granular Leukocytes



A neutrophil has small granules that stain light lilac and a nucleus with two to five lobes. An eosinophil's granules are slightly larger and stain reddish-orange, and its nucleus has two to three lobes. A basophil has large granules that stain dark blue to purple and a two-lobed nucleus.

The most common of all the leukocytes, **neutrophils** will normally comprise 50–70 percent of total leukocyte count. They are 10–12 μm in diameter, significantly larger than erythrocytes. They are called neutrophils because their granules show up most clearly with stains that are chemically neutral (neither acidic nor basic). The granules are numerous but quite fine and normally appear light lilac. The nucleus has a distinct lobed appearance and may have two to five lobes, the number increasing with the age of the cell. Older neutrophils have increasing numbers of lobes and are often referred to as **polymorphonuclear** (a nucleus with many forms), or simply "polys." Younger and immature neutrophils begin to develop lobes and are known as "bands."

Neutrophils are rapid responders to the site of infection and are efficient phagocytes with a preference for bacteria. Their granules include **lysozyme**, an enzyme capable of lysing, or breaking down, bacterial cell walls; oxidants such as hydrogen peroxide; and **defensins**, proteins that bind to and puncture bacterial and fungal plasma membranes, so that the cell contents leak out. Abnormally high counts of neutrophils indicate infection and/or inflammation, particularly triggered by bacteria, but are also found in burn patients and others experiencing unusual stress. A burn injury increases the proliferation of neutrophils in order to fight off infection that can result from the destruction of the barrier of the skin. Low counts may be caused by drug toxicity and other disorders, and may increase an individual's susceptibility to infection.

Eosinophils typically represent 2–4 percent of total leukocyte count. They are also 10–12 μm in diameter. The granules of eosinophils stain best with

an acidic stain known as eosin. The nucleus of the eosinophil will typically have two to three lobes and, if stained properly, the granules will have a distinct red to orange color.

The granules of eosinophils include antihistamine molecules, which counteract the activities of histamines, inflammatory chemicals produced by basophils and mast cells. Some eosinophil granules contain molecules toxic to parasitic worms, which can enter the body through the integument, or when an individual consumes raw or undercooked fish or meat. Eosinophils are also capable of phagocytosis and are particularly effective when antibodies bind to the target and form an antigen-antibody complex. High counts of eosinophils are typical of patients experiencing allergies, parasitic worm infestations, and some autoimmune diseases. Low counts may be due to drug toxicity and stress.

Basophils are the least common leukocytes, typically comprising less than one percent of the total leukocyte count. They are slightly smaller than neutrophils and eosinophils at 8–10 μm in diameter. The granules of basophils stain best with basic (alkaline) stains. Basophils contain large granules that pick up a dark blue stain and are so common they may make it difficult to see the two-lobed nucleus.

In general, basophils intensify the inflammatory response. They share this trait with mast cells. In the past, mast cells were considered to be basophils that left the circulation. However, this appears not to be the case, as the two cell types develop from different lineages.

The granules of basophils release histamines, which contribute to inflammation, and heparin, which opposes blood clotting. High counts of basophils are associated with allergies, parasitic infections, and hypothyroidism. Low counts are associated with pregnancy, stress, and hyperthyroidism.

Agranular Leukocytes

Agranular leukocytes contain smaller, less-visible granules in their cytoplasm than do granular leukocytes. The nucleus is simple in shape, sometimes with an indentation but without distinct lobes. There are two major types of agranulocytes: lymphocytes and monocytes (see [link]).

Lymphocytes are the only formed element of blood that arises from lymphoid stem cells. Although they form initially in the bone marrow, much of their subsequent development and reproduction occurs in the lymphatic tissues. Lymphocytes are the second most common type of leukocyte, accounting for about 20–30 percent of all leukocytes, and are essential for the immune response. The size range of lymphocytes is quite extensive, with some authorities recognizing two size classes and others three. Typically, the large cells are 10–14 μm and have a smaller nucleus-to-cytoplasm ratio and more granules. The smaller cells are typically 6–9 μm with a larger volume of nucleus to cytoplasm, creating a “halo” effect. A few cells may fall outside these ranges, at 14–17 μm. This finding has led to the three size range classification.

The three major groups of lymphocytes include natural killer cells, B cells, and T cells. **Natural killer (NK) cells** are capable of recognizing cells that do not express “self” proteins on their plasma membrane or that contain foreign or abnormal markers. These “nonself” cells include cancer cells, cells infected with a virus, and other cells with atypical surface proteins. Thus, they provide generalized, nonspecific immunity. The larger lymphocytes are typically NK cells.

B cells and T cells, also called **B lymphocytes** and **T lymphocytes**, play prominent roles in defending the body against specific pathogens (disease-causing microorganisms) and are involved in specific immunity. One form of B cells (plasma cells) produces the antibodies or immunoglobulins that bind to specific foreign or abnormal components of plasma membranes. This is also referred to as humoral (body fluid) immunity. T cells provide cellular-level immunity by physically attacking foreign or diseased cells. A **memory cell** is a variety of both B and T cells that forms after exposure to a pathogen and mounts rapid responses upon subsequent exposures. Unlike other leukocytes, memory cells live for many years. B cells undergo a maturation process in the bone marrow, whereas T cells undergo maturation

in the thymus. This site of the maturation process gives rise to the name B and T cells. The functions of lymphocytes are complex and will be covered in detail in the chapter covering the lymphatic system and immunity. Smaller lymphocytes are either B or T cells, although they cannot be differentiated in a normal blood smear.

Abnormally high lymphocyte counts are characteristic of viral infections as well as some types of cancer. Abnormally low lymphocyte counts are characteristic of prolonged (chronic) illness or immunosuppression, including that caused by HIV infection and drug therapies that often involve steroids.

Monocytes originate from myeloid stem cells. They normally represent 2–8 percent of the total leukocyte count. They are typically easily recognized by their large size of 12–20 μm and indented or horseshoe-shaped nuclei. Macrophages are monocytes that have left the circulation and phagocytize debris, foreign pathogens, worn-out erythrocytes, and many other dead, worn out, or damaged cells. Macrophages also release antimicrobial defensins and chemotactic chemicals that attract other leukocytes to the site of an infection. Some macrophages occupy fixed locations, whereas others wander through the tissue fluid.

Abnormally high counts of monocytes are associated with viral or fungal infections, tuberculosis, and some forms of leukemia and other chronic diseases. Abnormally low counts are typically caused by suppression of the bone marrow.

Lifecycle of Leukocytes

Most leukocytes have a relatively short lifespan, typically measured in hours or days. Production of all leukocytes begins in the bone marrow under the influence of CSFs and interleukins. Secondary production and maturation of lymphocytes occurs in specific regions of lymphatic tissue known as germinal centers. Lymphocytes are fully capable of mitosis and may produce clones of cells with identical properties. This capacity enables an individual to maintain immunity throughout life to many threats that have been encountered in the past.

Disorders of Leukocytes

Leukopenia is a condition in which too few leukocytes are produced. If this condition is pronounced, the individual may be unable to ward off disease. Excessive leukocyte proliferation is known as **leukocytosis**. Although leukocyte counts are high, the cells themselves are often nonfunctional, leaving the individual at increased risk for disease.

Leukemia is a cancer involving an abundance of leukocytes. It may involve only one specific type of leukocyte from either the myeloid line (myelocytic leukemia) or the lymphoid line (lymphocytic leukemia). In chronic leukemia, mature leukocytes accumulate and fail to die. In acute leukemia, there is an overproduction of young, immature leukocytes. In both conditions the cells do not function properly.

Lymphoma is a form of cancer in which masses of malignant T and/or B lymphocytes collect in lymph nodes, the spleen, the liver, and other tissues. As in leukemia, the malignant leukocytes do not function properly, and the patient is vulnerable to infection. Some forms of lymphoma tend to progress slowly and respond well to treatment. Others tend to progress quickly and require aggressive treatment, without which they are rapidly fatal.

Platelets

You may occasionally see platelets referred to as **thrombocytes**, but because this name suggests they are a type of cell, it is not accurate. A platelet is not a cell but rather a fragment of the cytoplasm of a cell called a **megakaryocyte** that is surrounded by a plasma membrane. Megakaryocytes are descended from myeloid stem cells (see [link]) and are large, typically 50–100 μm in diameter, and contain an enlarged, lobed nucleus. As noted earlier, thrombopoietin, a glycoprotein secreted by the kidneys and liver, stimulates the proliferation of megakaryoblasts, which mature into megakaryocytes. These remain within bone marrow tissue ([link]) and ultimately form platelet-precursor extensions that extend through the walls of bone marrow capillaries to release into the circulation thousands of cytoplasmic fragments, each enclosed by a bit of plasma membrane. These

enclosed fragments are platelets. Each megakarocyte releases 2000–3000 platelets during its lifespan. Following platelet release, megakaryocyte remnants, which are little more than a cell nucleus, are consumed by macrophages.

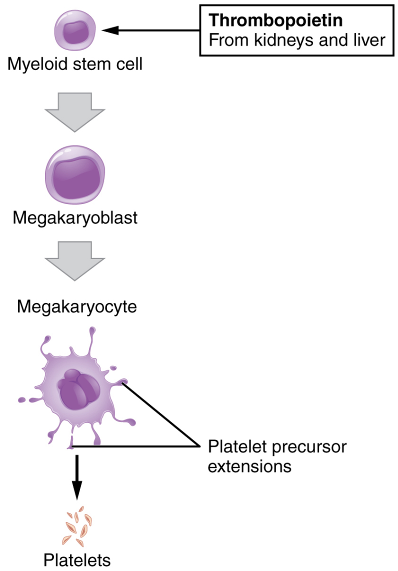
Platelets are relatively small, 2–4 μm in diameter, but numerous, with typically 150,000–160,000 per μL of blood. After entering the circulation, approximately one-third migrate to the spleen for storage for later release in response to any rupture in a blood vessel. They then become activated to perform their primary function, which is to limit blood loss. Platelets remain only about 10 days, then are phagocytized by macrophages.

Platelets are critical to hemostasis, the stoppage of blood flow following damage to a vessel. They also secrete a variety of growth factors essential for growth and repair of tissue, particularly connective tissue. Infusions of concentrated platelets are now being used in some therapies to stimulate healing.

Disorders of Platelets

Thrombocytosis is a condition in which there are too many platelets. This may trigger formation of unwanted blood clots (thrombosis), a potentially fatal disorder. If there is an insufficient number of platelets, called **thrombocytopenia**, blood may not clot properly, and excessive bleeding may result.

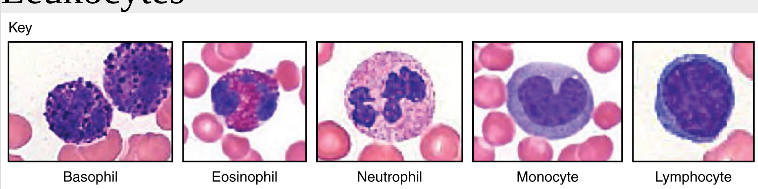
Platelets



Platelets are derived from cells called megakaryocytes.

Note:

Leukocytes



(Micrographs provided by the Regents of

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View University of Michigan Webscopes at http://virtualslides.med.umich.edu/Histology/Cardiovascular%20System/081-2_HISTO_40X.svs/view.apml?cwidth=860&cheight=733&chost=virtualslides.med.umich.edu&listview=1&title=&csis=1 and explore the blood slides in greater detail. The Webscope feature allows you to move the slides as you would with a mechanical stage. You can increase and decrease the magnification. There is a chance to review each of the leukocytes individually after you have attempted to identify them from the first two blood smears. In addition, there are a few multiple choice questions.

Are you able to recognize and identify the various formed elements? You will need to do this is a systematic manner, scanning along the image. The standard method is to use a grid, but this is not possible with this resource. Try constructing a simple table with each leukocyte type and then making a mark for each cell type you identify. Attempt to classify at least 50 and perhaps as many as 100 different cells. Based on the percentage of cells that you count, do the numbers represent a normal blood smear or does something appear to be abnormal?

Chapter Review

Leukocytes function in body defenses. They squeeze out of the walls of blood vessels through emigration or diapedesis, then may move through tissue fluid or become attached to various organs where they fight against pathogenic organisms, diseased cells, or other threats to health. Granular leukocytes, which include neutrophils, eosinophils, and basophils, originate with myeloid stem cells, as do the agranular monocytes. The other agranular leukocytes, NK cells, B cells, and T cells, arise from the lymphoid stem cell line. The most abundant leukocytes are the neutrophils, which are first responders to infections, especially with bacteria. About 20–30 percent of all leukocytes are lymphocytes, which are critical to the

body’s defense against specific threats. Leukemia and lymphoma are malignancies involving leukocytes. Platelets are fragments of cells known as megakaryocytes that dwell within the bone marrow. While many platelets are stored in the spleen, others enter the circulation and are essential for hemostasis; they also produce several growth factors important for repair and healing.

Interactive Link Questions

Exercise:

Problem:

[link] Are you able to recognize and identify the various formed elements? You will need to do this is a systematic manner, scanning along the image. The standard method is to use a grid, but this is not possible with this resource. Try constructing a simple table with each leukocyte type and then making a mark for each cell type you identify. Attempt to classify at least 50 and perhaps as many as 100 different cells. Based on the percentage of cells that you count, do the numbers represent a normal blood smear or does something appear to be abnormal?

Solution:

[link] This should appear to be a normal blood smear.

Review Questions

Exercise:

Problem:

The process by which leukocytes squeeze through adjacent cells in a blood vessel wall is called _________.

a. leukocytosis
b. positive chemotaxis

c. emigration
d. cytoplasmic extending

Solution:

C

Exercise:

Problem: Which of the following describes a neutrophil?

a. abundant, agranular, especially effective against cancer cells
b. abundant, granular, especially effective against bacteria
c. rare, agranular, releases antimicrobial defensins
d. rare, granular, contains multiple granules packed with histamine

---

Solution:

B

Exercise:

Problem: T and B lymphocytes ________.

a. are polymorphonuclear
b. are involved with specific immune function
c. proliferate excessively in leukopenia
d. are most active against parasitic worms

Solution:

B

Exercise:

Problem:

A patient has been experiencing severe, persistent allergy symptoms that are reduced when she takes an antihistamine. Before the treatment, this patient was likely to have had increased activity of which leukocyte?

a. basophils
b. neutrophils
c. monocytes
d. natural killer cells

Solution:

A

Exercise:

Problem: Thrombocytes are more accurately called ________.

a. clotting factors
b. megakaryoblasts
c. megakaryocytes
d. platelets

Solution:

D

Critical Thinking Questions

Exercise:

Problem:

One of the more common adverse effects of cancer chemotherapy is the destruction of leukocytes. Before his next scheduled chemotherapy treatment, a patient undergoes a blood test called an absolute neutrophil count (ANC), which reveals that his neutrophil count is 1900 cells per microliter. Would his healthcare team be likely to proceed with his chemotherapy treatment? Why?

Solution:

A neutrophil count below 1800 cells per microliter is considered abnormal. Thus, this patient's ANC is at the low end of the normal range and there would be no reason to delay chemotherapy. In clinical practice, most patients are given chemotherapy if their ANC is above 1000.

Exercise:

Problem:

A patient was admitted to the burn unit the previous evening suffering from a severe burn involving his left upper extremity and shoulder. A blood test reveals that he is experiencing leukocytosis. Why is this an expected finding?

Solution:

Any severe stress can increase the leukocyte count, resulting in leukocytosis. A burn is especially likely to increase the proliferation of leukocytes in order to ward off infection, a significant risk when the barrier function of the skin is destroyed.

Glossary

agranular leukocytes
: leukocytes with few granules in their cytoplasm; specifically, monocytes, lymphocytes, and NK cells

B lymphocytes
: (also, B cells) lymphocytes that defend the body against specific pathogens and thereby provide specific immunity

basophils
: granulocytes that stain with a basic (alkaline) stain and store histamine and heparin

defensins
: antimicrobial proteins released from neutrophils and macrophages that create openings in the plasma membranes to kill cells

diapedesis
: (also, emigration) process by which leukocytes squeeze through adjacent cells in a blood vessel wall to enter tissues

emigration
: (also, diapedesis) process by which leukocytes squeeze through adjacent cells in a blood vessel wall to enter tissues

eosinophils
: granulocytes that stain with eosin; they release antihistamines and are especially active against parasitic worms

granular leukocytes
: leukocytes with abundant granules in their cytoplasm; specifically, neutrophils, eosinophils, and basophils

leukemia
: cancer involving leukocytes

leukocyte
: (also, white blood cell) colorless, nucleated blood cell, the chief function of which is to protect the body from disease

leukocytosis
: excessive leukocyte proliferation

leukopenia

below-normal production of leukocytes

lymphocytes

agranular leukocytes of the lymphoid stem cell line, many of which function in specific immunity

lymphoma

form of cancer in which masses of malignant T and/or B lymphocytes collect in lymph nodes, the spleen, the liver, and other tissues

lysozyme

digestive enzyme with bactericidal properties

megakaryocyte

bone marrow cell that produces platelets

memory cell

type of B or T lymphocyte that forms after exposure to a pathogen

monocytes

agranular leukocytes of the myeloid stem cell line that circulate in the bloodstream; tissue monocytes are macrophages

natural killer (NK) cells

cytotoxic lymphocytes capable of recognizing cells that do not express “self” proteins on their plasma membrane or that contain foreign or abnormal markers; provide generalized, nonspecific immunity

neutrophils

granulocytes that stain with a neutral dye and are the most numerous of the leukocytes; especially active against bacteria

polymorphonuclear

having a lobed nucleus, as seen in some leukocytes

positive chemotaxis

process in which a cell is attracted to move in the direction of chemical stimuli

T lymphocytes
(also, T cells) lymphocytes that provide cellular-level immunity by physically attacking foreign or diseased cells

thrombocytes
platelets, one of the formed elements of blood that consists of cell fragments broken off from megakaryocytes

thrombocytopenia
condition in which there are too few platelets, resulting in abnormal bleeding (hemophilia)

thrombocytosis
condition in which there are too many platelets, resulting in abnormal clotting (thrombosis)

Hemostasis
By the end of this section, you will be able to:

- Describe the three mechanisms involved in hemostasis
- Explain how the extrinsic and intrinsic coagulation pathways lead to the common pathway, and the coagulation factors involved in each
- Discuss disorders affecting hemostasis

Platelets are key players in **hemostasis**, the process by which the body seals a ruptured blood vessel and prevents further loss of blood. Although rupture of larger vessels usually requires medical intervention, hemostasis is quite effective in dealing with small, simple wounds. There are three steps to the process: vascular spasm, the formation of a platelet plug, and coagulation (blood clotting). Failure of any of these steps will result in **hemorrhage**—excessive bleeding.

Vascular Spasm

When a vessel is severed or punctured, or when the wall of a vessel is damaged, vascular spasm occurs. In **vascular spasm**, the smooth muscle in the walls of the vessel contracts dramatically. This smooth muscle has both circular layers; larger vessels also have longitudinal layers. The circular layers tend to constrict the flow of blood, whereas the longitudinal layers, when present, draw the vessel back into the surrounding tissue, often making it more difficult for a surgeon to locate, clamp, and tie off a severed vessel. The vascular spasm response is believed to be triggered by several chemicals called endothelins that are released by vessel-lining cells and by pain receptors in response to vessel injury. This phenomenon typically lasts for up to 30 minutes, although it can last for hours.

Formation of the Platelet Plug

In the second step, platelets, which normally float free in the plasma, encounter the area of vessel rupture with the exposed underlying connective tissue and collagenous fibers. The platelets begin to clump together, become spiked and sticky, and bind to the exposed collagen and endothelial lining. This process is assisted by a glycoprotein in the blood plasma called von Willebrand factor, which helps stabilize the growing **platelet plug**. As platelets collect, they simultaneously release chemicals from their granules into the plasma that further contribute to hemostasis. Among the substances released by the platelets are:

- adenosine diphosphate (ADP), which helps additional platelets to adhere to the injury site, reinforcing and expanding the platelet plug
- serotonin, which maintains vasoconstriction

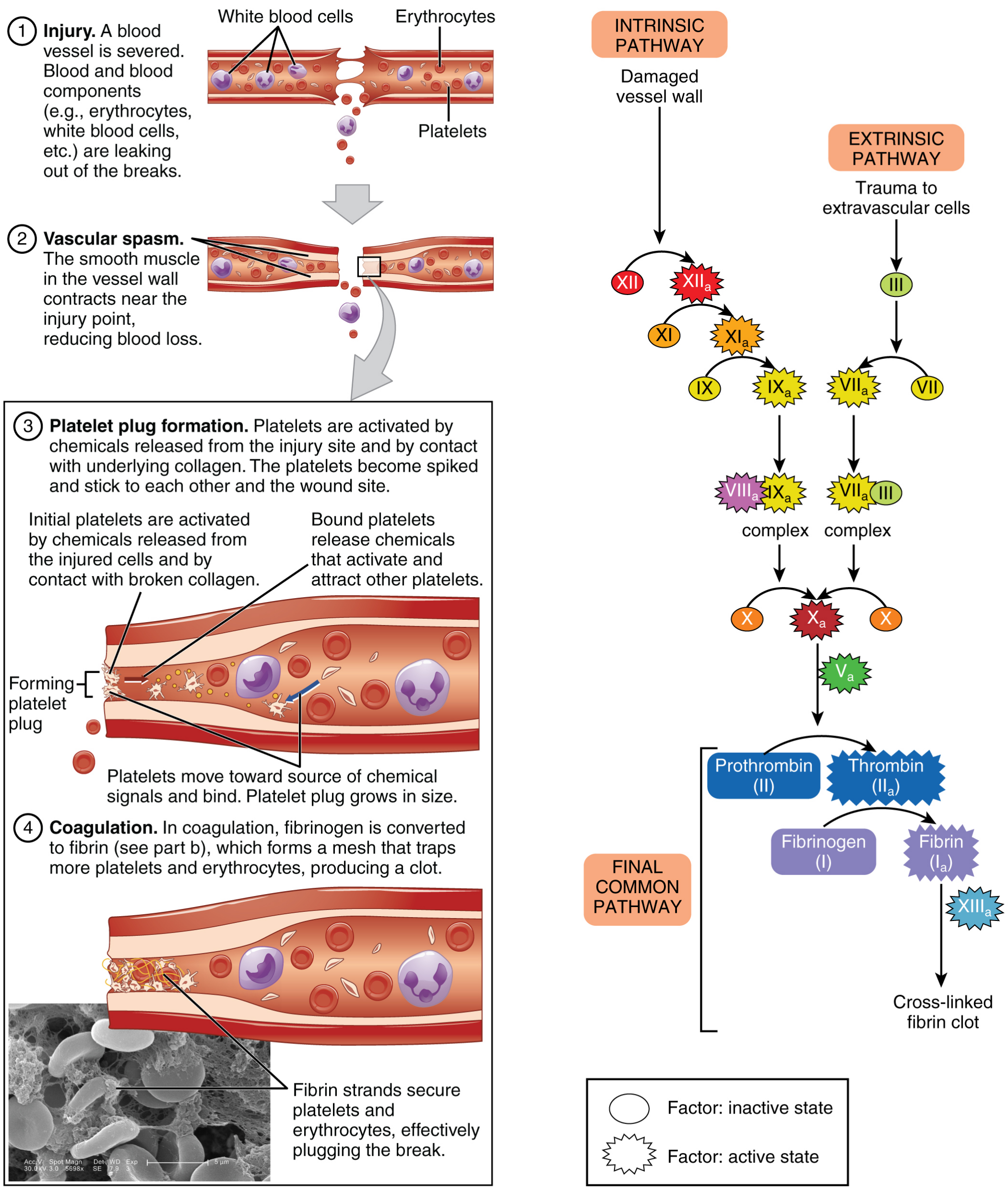
- prostaglandins and phospholipids, which also maintain vasoconstriction and help to activate further clotting chemicals, as discussed next

A platelet plug can temporarily seal a small opening in a blood vessel. Plug formation, in essence, buys the body time while more sophisticated and durable repairs are being made. In a similar manner, even modern naval warships still carry an assortment of wooden plugs to temporarily repair small breaches in their hulls until permanent repairs can be made.

Coagulation

Those more sophisticated and more durable repairs are collectively called **coagulation**, the formation of a blood clot. The process is sometimes characterized as a cascade, because one event prompts the next as in a multi-level waterfall. The result is the production of a gelatinous but robust clot made up of a mesh of **fibrin**—an insoluble filamentous protein derived from fibrinogen, the plasma protein introduced earlier—in which platelets and blood cells are trapped. [link] summarizes the three steps of hemostasis.

Hemostasis



(a) The general steps of clotting

(b) Fibrin synthesis cascade

(a) An injury to a blood vessel initiates the process of hemostasis. Blood clotting involves three steps. First, vascular spasm constricts the flow of blood. Next, a platelet plug forms to temporarily seal small openings in the vessel. Coagulation then enables the repair of the vessel wall once the leakage of blood has stopped. (b) The synthesis of fibrin in blood clots involves either an intrinsic pathway or an extrinsic pathway, both of which lead to a common pathway. (credit a: Kevin MacKenzie)

Clotting Factors Involved in Coagulation

In the coagulation cascade, chemicals called **clotting factors** (or coagulation factors) prompt reactions that activate still more coagulation factors. The process is complex, but is initiated along two basic pathways:

- The extrinsic pathway, which normally is triggered by trauma.
- The intrinsic pathway, which begins in the bloodstream and is triggered by internal damage to the wall of the vessel.

Both of these merge into a third pathway, referred to as the common pathway (see [link]**b**). All three pathways are dependent upon the 12 known clotting factors, including Ca^{2+} and vitamin K ([link]). Clotting factors are secreted primarily by the liver and the platelets. The liver requires the fat-soluble vitamin K to produce many of them. Vitamin K (along with biotin and folate) is somewhat unusual among vitamins in that it is not only consumed in the diet but is also synthesized by bacteria residing in the large intestine. The calcium ion, considered factor IV, is derived from the diet and from the breakdown of bone. Some recent evidence indicates that activation of various clotting factors occurs on specific receptor sites on the surfaces of platelets.

The 12 clotting factors are numbered I through XIII according to the order of their discovery. Factor VI was once believed to be a distinct clotting factor, but is now thought to be identical to factor V. Rather than renumber the other factors, factor VI was allowed to remain as a placeholder and also a reminder that knowledge changes over time.

Clotting Factors				
Factor number	**Name**	**Type of molecule**	**Source**	**Pathway(s)**
I	Fibrinogen	Plasma protein	Liver	Common; converted into fibrin

Clotting Factors				
Factor number	**Name**	**Type of molecule**	**Source**	**Pathway(s)**
II	Prothrombin	Plasma protein	Liver*	Common; converted into thrombin
III	Tissue thromboplastin or tissue factor	Lipoprotein mixture	Damaged cells and platelets	Extrinsic
IV	Calcium ions	Inorganic ions in plasma	Diet, platelets, bone matrix	Entire process
V	Proaccelerin	Plasma protein	Liver, platelets	Extrinsic and intrinsic
VI	Not used	Not used	Not used	Not used
VII	Proconvertin	Plasma protein	Liver *	Extrinsic
VIII	Antihemolytic factor A	Plasma protein factor	Platelets and endothelial cells	Intrinsic; deficiency results in hemophilia A
IX	Antihemolytic factor B (plasma thromboplastin component)	Plasma protein	Liver*	Intrinsic; deficiency results in hemophilia B

Clotting Factors				
Factor number	**Name**	**Type of molecule**	**Source**	**Pathway(s)**
X	Stuart–Prower factor (thrombokinase)	Protein	Liver*	Extrinsic and intrinsic
XI	Antihemolytic factor C (plasma thromboplastin antecedent)	Plasma protein	Liver	Intrinsic; deficiency results in hemophilia C
XII	Hageman factor	Plasma protein	Liver	Intrinsic; initiates clotting in vitro also activates plasmin
XIII	Fibrin-stabilizing factor	Plasma protein	Liver, platelets	Stabilizes fibrin; slows fibrinolysis

*Vitamin K required.

Extrinsic Pathway

The quicker responding and more direct **extrinsic pathway** (also known as the **tissue factor** pathway) begins when damage occurs to the surrounding tissues, such as in a traumatic injury. Upon contact with blood plasma, the damaged extravascular cells, which are extrinsic to the bloodstream, release factor III (thromboplastin). Sequentially, Ca^{2+} then factor VII (proconvertin), which is activated by factor III, are added, forming an enzyme complex. This enzyme complex leads to activation of factor X (Stuart–Prower factor), which activates the common pathway discussed below. The events in the extrinsic pathway are completed in a matter of seconds.

Intrinsic Pathway

The **intrinsic pathway** (also known as the contact activation pathway) is longer and more complex. In this case, the factors involved are intrinsic to (present within) the bloodstream. The pathway can be prompted by damage to the tissues, resulting from internal factors such as arterial disease; however, it is most often initiated when factor XII (Hageman factor) comes into contact with foreign materials, such as when a blood sample is put into a glass test tube. Within the body, factor XII is typically activated when it encounters negatively charged molecules, such as inorganic polymers and phosphate produced earlier in the series of intrinsic pathway reactions. Factor XII sets off a series of reactions that in turn activates factor XI (antihemolytic factor C or plasma thromboplastin antecedent) then factor IX (antihemolytic factor B or plasma thromboplasmin). In the meantime, chemicals released by the platelets increase the rate of these activation reactions. Finally, factor VIII (antihemolytic factor A) from the platelets and endothelial cells combines with factor IX (antihemolytic factor B or plasma thromboplasmin) to form an enzyme complex that activates factor X (Stuart–Prower factor or thrombokinase), leading to the common pathway. The events in the intrinsic pathway are completed in a few minutes.

Common Pathway

Both the intrinsic and extrinsic pathways lead to the **common pathway**, in which fibrin is produced to seal off the vessel. Once factor X has been activated by either the intrinsic or extrinsic pathway, the enzyme prothrombinase converts factor II, the inactive enzyme prothrombin, into the active enzyme **thrombin**. (Note that if the enzyme thrombin were not normally in an inactive form, clots would form spontaneously, a condition not consistent with life.) Then, thrombin converts factor I, the soluble fibrinogen, into the insoluble fibrin protein strands. Factor XIII then stabilizes the fibrin clot.

Fibrinolysis

The stabilized clot is acted upon by contractile proteins within the platelets. As these proteins contract, they pull on the fibrin threads, bringing the edges of the clot more tightly together, somewhat as we do when tightening loose shoelaces (see [link]**a**). This process also wrings out of the clot a small amount of fluid called **serum**, which is blood plasma without its clotting factors.

To restore normal blood flow as the vessel heals, the clot must eventually be removed. **Fibrinolysis** is the gradual degradation of the clot. Again, there is a fairly complicated

series of reactions that involves factor XII and protein-catabolizing enzymes. During this process, the inactive protein plasminogen is converted into the active **plasmin**, which gradually breaks down the fibrin of the clot. Additionally, bradykinin, a vasodilator, is released, reversing the effects of the serotonin and prostaglandins from the platelets. This allows the smooth muscle in the walls of the vessels to relax and helps to restore the circulation.

Plasma Anticoagulants

An **anticoagulant** is any substance that opposes coagulation. Several circulating plasma anticoagulants play a role in limiting the coagulation process to the region of injury and restoring a normal, clot-free condition of blood. For instance, a cluster of proteins collectively referred to as the protein C system inactivates clotting factors involved in the intrinsic pathway. TFPI (tissue factor pathway inhibitor) inhibits the conversion of the inactive factor VII to the active form in the extrinsic pathway. **Antithrombin** inactivates factor X and opposes the conversion of prothrombin (factor II) to thrombin in the common pathway. And as noted earlier, basophils release **heparin**, a short-acting anticoagulant that also opposes prothrombin. Heparin is also found on the surfaces of cells lining the blood vessels. A pharmaceutical form of heparin is often administered therapeutically, for example, in surgical patients at risk for blood clots.

Note:

View these animations to explore the intrinsic, extrinsic, and common pathways that are involved the process of coagulation. The coagulation cascade restores hemostasis by activating coagulation factors in the presence of an injury. How does the endothelium of the blood vessel walls prevent the blood from coagulating as it flows through the blood vessels?

Disorders of Clotting

Either an insufficient or an excessive production of platelets can lead to severe disease or death. As discussed earlier, an insufficient number of platelets, called thrombocytopenia, typically results in the inability of blood to form clots. This can lead to excessive bleeding, even from minor wounds.

Another reason for failure of the blood to clot is the inadequate production of functional amounts of one or more clotting factors. This is the case in the genetic disorder **hemophilia**, which is actually a group of related disorders, the most common of which is hemophilia A, accounting for approximately 80 percent of cases. This disorder results in the inability to synthesize sufficient quantities of factor VIII. Hemophilia B is the second most common form, accounting for approximately 20 percent of cases. In this case, there is a deficiency of factor IX. Both of these defects are linked to the X chromosome and are typically passed from a healthy (carrier) mother to her male offspring, since males are XY. Females would need to inherit a defective gene from each parent to manifest the disease, since they are XX. Patients with hemophilia bleed from even minor internal and external wounds, and leak blood into joint spaces after exercise and into urine and stool. Hemophilia C is a rare condition that is triggered by an autosomal (not sex) chromosome that renders factor XI nonfunctional. It is not a true recessive condition, since even individuals with a single copy of the mutant gene show a tendency to bleed. Regular infusions of clotting factors isolated from healthy donors can help prevent bleeding in hemophiliac patients. At some point, genetic therapy will become a viable option.

In contrast to the disorders characterized by coagulation failure is thrombocytosis, also mentioned earlier, a condition characterized by excessive numbers of platelets that increases the risk for excessive clot formation, a condition known as **thrombosis**. A **thrombus** (plural = thrombi) is an aggregation of platelets, erythrocytes, and even WBCs typically trapped within a mass of fibrin strands. While the formation of a clot is normal following the hemostatic mechanism just described, thrombi can form within an intact or only slightly damaged blood vessel. In a large vessel, a thrombus will adhere to the vessel wall and decrease the flow of blood, and is referred to as a mural thrombus. In a small vessel, it may actually totally block the flow of blood and is termed an occlusive thrombus. Thrombi are most commonly caused by vessel damage to the endothelial lining, which activates the clotting mechanism. These may include venous stasis, when blood in the veins, particularly in the legs, remains stationary for long periods. This is one of the dangers of long airplane flights in crowded conditions and may lead to deep vein thrombosis or atherosclerosis, an accumulation of debris in arteries. Thrombophilia, also called hypercoagulation, is a condition in which there is a tendency to form thrombosis. This may be familial (genetic) or acquired. Acquired forms include the autoimmune disease lupus, immune reactions to heparin, polycythemia vera, thrombocytosis, sickle cell disease, pregnancy, and even obesity. A thrombus can seriously impede blood flow to or from

a region and will cause a local increase in blood pressure. If flow is to be maintained, the heart will need to generate a greater pressure to overcome the resistance.

When a portion of a thrombus breaks free from the vessel wall and enters the circulation, it is referred to as an **embolus**. An embolus that is carried through the bloodstream can be large enough to block a vessel critical to a major organ. When it becomes trapped, an embolus is called an embolism. In the heart, brain, or lungs, an embolism may accordingly cause a heart attack, a stroke, or a pulmonary embolism. These are medical emergencies.

Among the many known biochemical activities of aspirin is its role as an anticoagulant. Aspirin (acetylsalicylic acid) is very effective at inhibiting the aggregation of platelets. It is routinely administered during a heart attack or stroke to reduce the adverse effects. Physicians sometimes recommend that patients at risk for cardiovascular disease take a low dose of aspirin on a daily basis as a preventive measure. However, aspirin can also lead to serious side effects, including increasing the risk of ulcers. A patient is well advised to consult a physician before beginning any aspirin regimen.

A class of drugs collectively known as thrombolytic agents can help speed up the degradation of an abnormal clot. If a thrombolytic agent is administered to a patient within 3 hours following a thrombotic stroke, the patient’s prognosis improves significantly. However, some strokes are not caused by thrombi, but by hemorrhage. Thus, the cause must be determined before treatment begins. Tissue plasminogen activator is an enzyme that catalyzes the conversion of plasminogen to plasmin, the primary enzyme that breaks down clots. It is released naturally by endothelial cells but is also used in clinical medicine. New research is progressing using compounds isolated from the venom of some species of snakes, particularly vipers and cobras, which may eventually have therapeutic value as thrombolytic agents.

Chapter Review

Hemostasis is the physiological process by which bleeding ceases. Hemostasis involves three basic steps: vascular spasm, the formation of a platelet plug, and coagulation, in which clotting factors promote the formation of a fibrin clot. Fibrinolysis is the process in which a clot is degraded in a healing vessel. Anticoagulants are substances that oppose coagulation. They are important in limiting the extent and duration of clotting. Inadequate clotting can result from too few platelets, or inadequate production of clotting factors, for instance, in the genetic disorder hemophilia. Excessive clotting, called thrombosis, can be caused by excessive numbers of platelets. A thrombus is a collection of fibrin, platelets, and erythrocytes that has accumulated along the lining of a blood vessel, whereas an

embolus is a thrombus that has broken free from the vessel wall and is circulating in the bloodstream.

Interactive Link Questions

Exercise:

Problem:

View these animations to explore the intrinsic, extrinsic, and common pathways that are involved the process of coagulation. The coagulation cascade restores hemostasis by activating coagulation factors in the presence of an injury. How does the endothelium of the blood vessel walls prevent the blood from coagulating as it flows through the blood vessels?

Solution:

Clotting factors flow through the blood vessels in their inactive state. The endothelium does not have thrombogenic tissue factor to activate clotting factors.

Review Questions

Exercise:

Problem: The first step in hemostasis is ________.

a. vascular spasm
b. conversion of fibrinogen to fibrin
c. activation of the intrinsic pathway
d. activation of the common pathway

Solution:

A

Exercise:

Problem: Prothrombin is converted to thrombin during the ________.

a. intrinsic pathway
b. extrinsic pathway

c. common pathway
d. formation of the platelet plug

Solution:

C

Exercise:

Problem: Hemophilia is characterized by ________.

a. inadequate production of heparin
b. inadequate production of clotting factors
c. excessive production of fibrinogen
d. excessive production of platelets

Solution:

B

Critical Thinking Questions

Exercise:

Problem:

A lab technician collects a blood sample in a glass tube. After about an hour, she harvests serum to continue her blood analysis. Explain what has happened during the hour that the sample was in the glass tube.

Solution:

When blood contacts glass, the intrinsic coagulation pathway is initiated. This leads to the common pathway, and the blood clots. Within about 30 minutes, the clot begins to shrink. After an hour, it is about half its original size. Its heavier weight will cause it to fall to the bottom of the tube during centrifugation, allowing the lab technician to harvest the serum remaining at the top.

Exercise:

Problem:

Explain why administration of a thrombolytic agent is a first intervention for someone who has suffered a thrombotic stroke.

Solution:

In a thrombotic stroke, a blood vessel to the brain has been blocked by a thrombus, an aggregation of platelets and erythrocytes within a blood vessel. A thrombolytic agent is a medication that promotes the breakup of thrombi.

Glossary

anticoagulant
: substance such as heparin that opposes coagulation

antithrombin
: anticoagulant that inactivates factor X and opposes the conversion of prothrombin (factor II) into thrombin in the common pathway

clotting factors
: group of 12 identified substances active in coagulation

coagulation
: formation of a blood clot; part of the process of hemostasis

common pathway
: final coagulation pathway activated either by the intrinsic or the extrinsic pathway, and ending in the formation of a blood clot

embolus
: thrombus that has broken free from the blood vessel wall and entered the circulation

extrinsic pathway
: initial coagulation pathway that begins with tissue damage and results in the activation of the common pathway

fibrin
: insoluble, filamentous protein that forms the structure of a blood clot

fibrinolysis

gradual degradation of a blood clot

hemophilia
genetic disorder characterized by inadequate synthesis of clotting factors

hemorrhage
excessive bleeding

hemostasis
physiological process by which bleeding ceases

heparin
short-acting anticoagulant stored in mast cells and released when tissues are injured, opposes prothrombin

intrinsic pathway
initial coagulation pathway that begins with vascular damage or contact with foreign substances, and results in the activation of the common pathway

plasmin
blood protein active in fibrinolysis

platelet plug
accumulation and adhesion of platelets at the site of blood vessel injury

serum
blood plasma that does not contain clotting factors

thrombin
enzyme essential for the final steps in formation of a fibrin clot

thrombosis
excessive clot formation

thrombus
aggregation of fibrin, platelets, and erythrocytes in an intact artery or vein

tissue factor
protein thromboplastin, which initiates the extrinsic pathway when released in response to tissue damage

vascular spasm
initial step in hemostasis, in which the smooth muscle in the walls of the ruptured or damaged blood vessel contracts

Blood Typing
By the end of this section, you will be able to:

- Describe the two basic physiological consequences of transfusion of incompatible blood
- Compare and contrast ABO and Rh blood groups
- Identify which blood groups may be safely transfused into patients with different ABO types
- Discuss the pathophysiology of hemolytic disease of the newborn

Blood transfusions in humans were risky procedures until the discovery of the major human blood groups by Karl Landsteiner, an Austrian biologist and physician, in 1900. Until that point, physicians did not understand that death sometimes followed blood transfusions, when the type of donor blood infused into the patient was incompatible with the patient's own blood. Blood groups are determined by the presence or absence of specific marker molecules on the plasma membranes of erythrocytes. With their discovery, it became possible for the first time to match patient-donor blood types and prevent transfusion reactions and deaths.

Antigens, Antibodies, and Transfusion Reactions

Antigens are substances that the body does not recognize as belonging to the "self" and that therefore trigger a defensive response from the leukocytes of the immune system. (Seek more content for additional information on immunity.) Here, we will focus on the role of immunity in blood transfusion reactions. With RBCs in particular, you may see the antigens referred to as isoantigens or agglutinogens (surface antigens) and the antibodies referred to as isoantibodies or agglutinins. In this chapter, we will use the more common terms antigens and antibodies.

Antigens are generally large proteins, but may include other classes of organic molecules, including carbohydrates, lipids, and nucleic acids. Following an infusion of incompatible blood, erythrocytes with foreign antigens appear in the bloodstream and trigger an immune response. Proteins called antibodies (immunoglobulins), which are produced by certain B lymphocytes called plasma cells, attach to the antigens on the plasma membranes of the infused erythrocytes and cause them to adhere to one another.

- Because the arms of the Y-shaped antibodies attach randomly to more than one nonself erythrocyte surface, they form clumps of erythrocytes. This process is called **agglutination**.

- The clumps of erythrocytes block small blood vessels throughout the body, depriving tissues of oxygen and nutrients.
- As the erythrocyte clumps are degraded, in a process called **hemolysis**, their hemoglobin is released into the bloodstream. This hemoglobin travels to the kidneys, which are responsible for filtration of the blood. However, the load of hemoglobin released can easily overwhelm the kidney’s capacity to clear it, and the patient can quickly develop kidney failure.

More than 50 antigens have been identified on erythrocyte membranes, but the most significant in terms of their potential harm to patients are classified in two groups: the ABO blood group and the Rh blood group.

The ABO Blood Group

Although the **ABO blood group** name consists of three letters, ABO blood typing designates the presence or absence of just two antigens, A and B. Both are glycoproteins. People whose erythrocytes have A antigens on their erythrocyte membrane surfaces are designated blood type A, and those whose erythrocytes have B antigens are blood type B. People can also have both A and B antigens on their erythrocytes, in which case they are blood type AB. People with neither A nor B antigens are designated blood type O. ABO blood types are genetically determined.

Normally the body must be exposed to a foreign antigen before an antibody can be produced. This is not the case for the ABO blood group. Individuals with type A blood—without any prior exposure to incompatible blood—have preformed antibodies to the B antigen circulating in their blood plasma. These antibodies, referred to as anti-B antibodies, will cause agglutination and hemolysis if they ever encounter erythrocytes with B antigens. Similarly, an individual with type B blood has pre-formed anti-A antibodies. Individuals with type AB blood, which has both antigens, do not have preformed antibodies to either of these. People with type O blood lack antigens A and B on their erythrocytes, but both anti-A and anti-B antibodies circulate in their blood plasma.

Rh Blood Groups

The **Rh blood group** is classified according to the presence or absence of a second erythrocyte antigen identified as Rh. (It was first discovered in a type of primate known as a rhesus macaque, which is often used in research, because its blood is similar to that of humans.) Although dozens of Rh antigens have been identified,

only one, designated D, is clinically important. Those who have the Rh D antigen present on their erythrocytes—about 85 percent of Americans—are described as Rh positive (Rh^+) and those who lack it are Rh negative (Rh^-). Note that the Rh group is distinct from the ABO group, so any individual, no matter their ABO blood type, may have or lack this Rh antigen. When identifying a patient's blood type, the Rh group is designated by adding the word positive or negative to the ABO type. For example, A positive (A^+) means ABO group A blood with the Rh antigen present, and AB negative (AB^-) means ABO group AB blood without the Rh antigen.

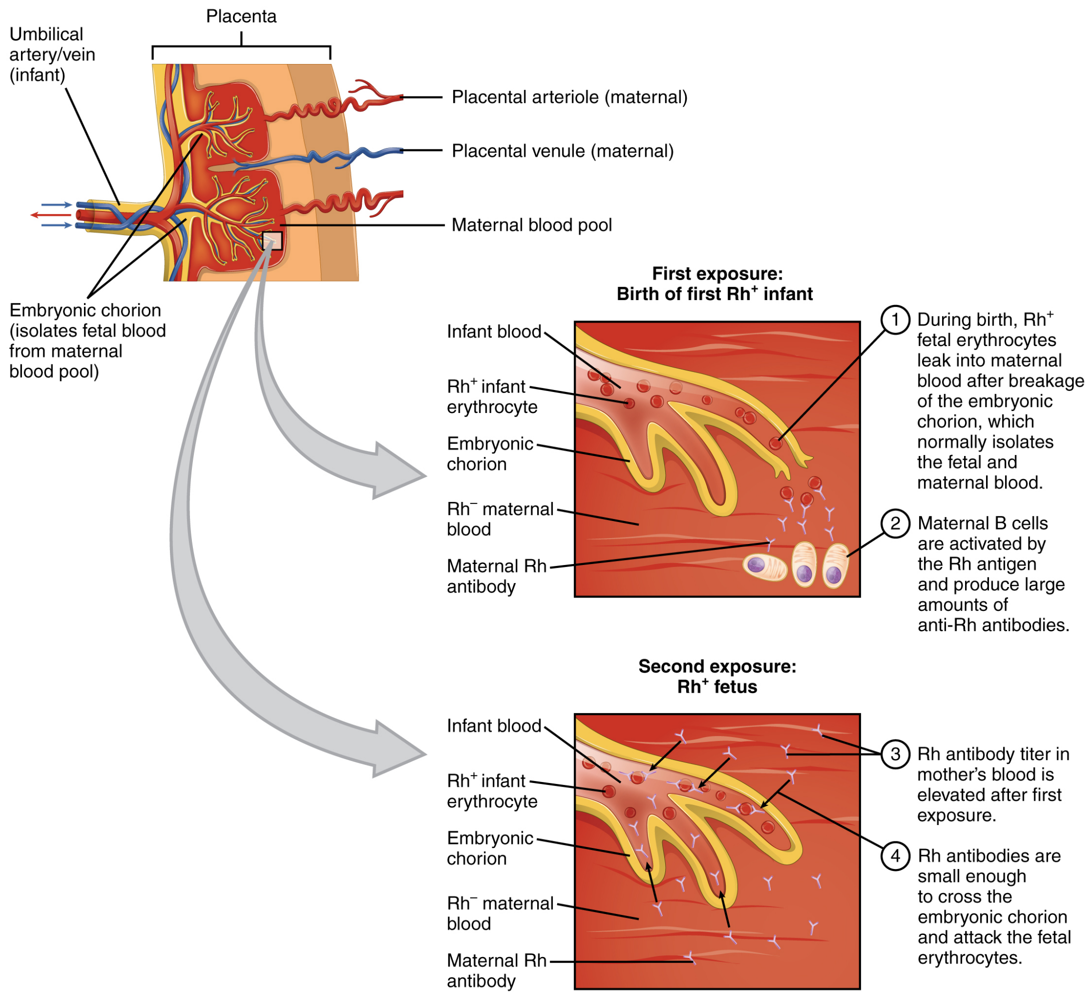
[link] summarizes the distribution of the ABO and Rh blood types within the United States.

Summary of ABO and Rh Blood Types within the United States				
Blood Type	**African-Americans**	**Asian-Americans**	**Caucasian-Americans**	**Latino/Latina-Americans**
A^+	24	27	33	29
A^-	2	0.5	7	2
B^+	18	25	9	9
B^-	1	0.4	2	1
AB^+	4	7	3	2
AB^-	0.3	0.1	1	0.2
O^+	47	39	37	53
O^-	4	1	8	4

In contrast to the ABO group antibodies, which are preformed, antibodies to the Rh antigen are produced only in Rh^- individuals after exposure to the antigen. This

process, called sensitization, occurs following a transfusion with Rh-incompatible blood or, more commonly, with the birth of an Rh^+ baby to an Rh^- mother. Problems are rare in a first pregnancy, since the baby's Rh^+ cells rarely cross the placenta (the organ of gas and nutrient exchange between the baby and the mother). However, during or immediately after birth, the Rh^- mother can be exposed to the baby's Rh^+ cells ([link]). Research has shown that this occurs in about 13−14 percent of such pregnancies. After exposure, the mother's immune system begins to generate anti-Rh antibodies. If the mother should then conceive another Rh^+ baby, the Rh antibodies she has produced can cross the placenta into the fetal bloodstream and destroy the fetal RBCs. This condition, known as **hemolytic disease of the newborn (HDN)** or erythroblastosis fetalis, may cause anemia in mild cases, but the agglutination and hemolysis can be so severe that without treatment the fetus may die in the womb or shortly after birth.

Erythroblastosis Fetalis



The first exposure of an Rh^- mother to Rh^+ erythrocytes during pregnancy induces sensitization. Anti-Rh antibodies begin to

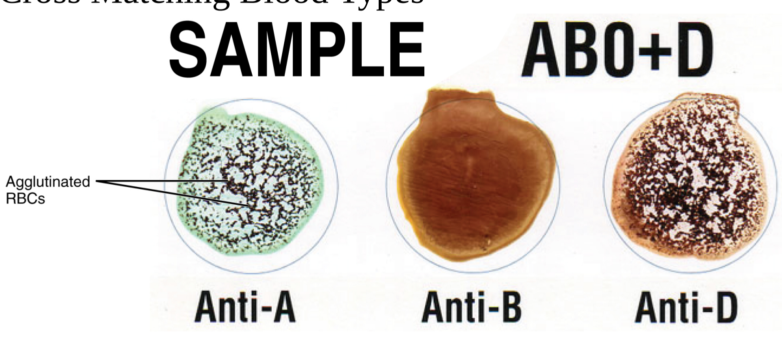
circulate in the mother's bloodstream. A second exposure occurs with a subsequent pregnancy with an Rh^+ fetus in the uterus. Maternal anti-Rh antibodies may cross the placenta and enter the fetal bloodstream, causing agglutination and hemolysis of fetal erythrocytes.

A drug known as RhoGAM, short for Rh immune globulin, can temporarily prevent the development of Rh antibodies in the Rh^- mother, thereby averting this potentially serious disease for the fetus. RhoGAM antibodies destroy any fetal Rh^+ erythrocytes that may cross the placental barrier. RhoGAM is normally administered to Rh^- mothers during weeks 26−28 of pregnancy and within 72 hours following birth. It has proven remarkably effective in decreasing the incidence of HDN. Earlier we noted that the incidence of HDN in an Rh^+ subsequent pregnancy to an Rh^- mother is about 13–14 percent without preventive treatment. Since the introduction of RhoGAM in 1968, the incidence has dropped to about 0.1 percent in the United States.

Determining ABO Blood Types

Clinicians are able to determine a patient's blood type quickly and easily using commercially prepared antibodies. An unknown blood sample is allocated into separate wells. Into one well a small amount of anti-A antibody is added, and to another a small amount of anti-B antibody. If the antigen is present, the antibodies will cause visible agglutination of the cells ([link]). The blood should also be tested for Rh antibodies.

Cross Matching Blood Types



This sample of a commercially produced "bedside" card enables quick typing of both a recipient's and donor's blood before transfusion. The card contains three reaction sites or wells.

One is coated with an anti-A antibody, one with an anti-B antibody, and one with an anti-D antibody (tests for the presence of Rh factor D). Mixing a drop of blood and saline into each well enables the blood to interact with a preparation of type-specific antibodies, also called anti-seras. Agglutination of RBCs in a given site indicates a positive identification of the blood antigens, in this case A and Rh antigens for blood type A^+. For the purpose of transfusion, the donor's and recipient's blood types must match.

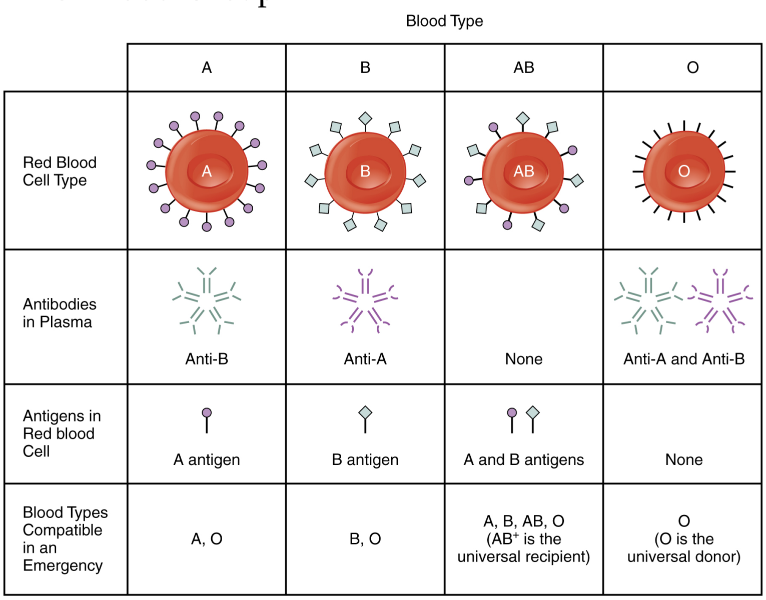
ABO Transfusion Protocols

To avoid transfusion reactions, it is best to transfuse only matching blood types; that is, a type B^+ recipient should ideally receive blood only from a type B^+ donor and so on. That said, in emergency situations, when acute hemorrhage threatens the patient's life, there may not be time for cross matching to identify blood type. In these cases, blood from a **universal donor**—an individual with type O^- blood—may be transfused. Recall that type O erythrocytes do not display A or B antigens. Thus, anti-A or anti-B antibodies that might be circulating in the patient's blood plasma will not encounter any erythrocyte surface antigens on the donated blood and therefore will not be provoked into a response. One problem with this designation of universal donor is if the O^- individual had prior exposure to Rh antigen, Rh antibodies may be present in the donated blood. Also, introducing type O blood into an individual with type A, B, or AB blood will nevertheless introduce antibodies against both A and B antigens, as these are always circulating in the type O blood plasma. This may cause problems for the recipient, but because the volume of blood transfused is much lower than the volume of the patient's own blood, the adverse effects of the relatively few infused plasma antibodies are typically limited. Rh factor also plays a role. If Rh^- individuals receiving blood have had prior exposure to Rh antigen, antibodies for this antigen may be present in the blood and trigger agglutination to some degree. Although it is always preferable to cross match a patient's blood before transfusing, in a true life-threatening emergency situation, this is not always possible, and these procedures may be implemented.

A patient with blood type AB^+ is known as the **universal recipient**. This patient can theoretically receive any type of blood, because the patient's own blood—having both A and B antigens on the erythrocyte surface—does not produce anti-A or anti-B antibodies. In addition, an Rh^+ patient can receive both Rh^+ and Rh^- blood. However, keep in mind that the donor's blood will contain circulating antibodies, again with possible negative implications. [link] summarizes the blood types and compatibilities.

At the scene of multiple-vehicle accidents, military engagements, and natural or human-caused disasters, many victims may suffer simultaneously from acute hemorrhage, yet type O blood may not be immediately available. In these circumstances, medics may at least try to replace some of the volume of blood that has been lost. This is done by intravenous administration of a saline solution that provides fluids and electrolytes in proportions equivalent to those of normal blood plasma. Research is ongoing to develop a safe and effective artificial blood that would carry out the oxygen-carrying function of blood without the RBCs, enabling transfusions in the field without concern for incompatibility. These blood substitutes normally contain hemoglobin- as well as perfluorocarbon-based oxygen carriers.

ABO Blood Group



This chart summarizes the characteristics of the blood types in the ABO blood group. See the text for more on the concept of a universal donor or recipient.

Chapter Review

Antigens are nonself molecules, usually large proteins, which provoke an immune response. In transfusion reactions, antibodies attach to antigens on the surfaces of erythrocytes and cause agglutination and hemolysis. ABO blood group antigens are designated A and B. People with type A blood have A antigens on their erythrocytes, whereas those with type B blood have B antigens. Those with AB blood have both A and B antigens, and those with type O blood have neither A nor B antigens. The blood plasma contains preformed antibodies against the antigens not present on a person’s erythrocytes.

A second group of blood antigens is the Rh group, the most important of which is Rh D. People with Rh^- blood do not have this antigen on their erythrocytes, whereas those who are Rh^+ do. About 85 percent of Americans are Rh^+. When a woman who is Rh^- becomes pregnant with an Rh^+ fetus, her body may begin to produce anti-Rh antibodies. If she subsequently becomes pregnant with a second Rh^+ fetus and is not treated preventively with RhoGAM, the fetus will be at risk for an antigen-antibody reaction, including agglutination and hemolysis. This is known as hemolytic disease of the newborn.

Cross matching to determine blood type is necessary before transfusing blood, unless the patient is experiencing hemorrhage that is an immediate threat to life, in which case type O^- blood may be transfused.

Review Questions

Exercise:

Problem:

The process in which antibodies attach to antigens, causing the formation of masses of linked cells, is called _________.

a. sensitization
b. coagulation
c. agglutination
d. hemolysis

Solution:

C

Exercise:

Problem: People with ABO blood type O ________.

a. have both antigens A and B on their erythrocytes
b. lack both antigens A and B on their erythrocytes
c. have neither anti-A nor anti-B antibodies circulating in their blood plasma
d. are considered universal recipients

Solution:

B

Exercise:

Problem:

Hemolytic disease of the newborn is a risk during a subsequent pregnancy in which ________.

a. a type AB mother is carrying a type O fetus
b. a type O mother is carrying a type AB fetus
c. an Rh^+ mother is carrying an Rh^- fetus
d. an Rh^- mother is carrying a second Rh^+ fetus

Solution:

D

Critical Thinking Questions

Exercise:

Problem:

Following a motor vehicle accident, a patient is rushed to the emergency department with multiple traumatic injuries, causing severe bleeding. The patient’s condition is critical, and there is no time for determining his blood type. What type of blood is transfused, and why?

Solution:

In emergency situations, blood type O^- will be infused until cross matching can be done. Blood type O^- is called the universal donor blood because the erythrocytes have neither A nor B antigens on their surface, and the Rh factor is negative.

Exercise:

Problem:

In preparation for a scheduled surgery, a patient visits the hospital lab for a blood draw. The technician collects a blood sample and performs a test to determine its type. She places a sample of the patient's blood in two wells. To the first well she adds anti-A antibody. To the second she adds anti-B antibody. Both samples visibly agglutinate. Has the technician made an error, or is this a normal response? If normal, what blood type does this indicate?

Solution:

The lab technician has not made an error. Blood type AB has both A and B surface antigens, and neither anti-A nor anti-B antibodies circulating in the plasma. When anti-A antibodies (added to the first well) contact A antigens on AB erythrocytes, they will cause agglutination. Similarly, when anti-B antibodies contact B antigens on AB erythrocytes, they will cause agglutination.

References

American Red Cross (US). Blood types [Internet]. c2013 [cited 2013 Apr 3]. Available from: http://www.redcrossblood.org/learn-about-blood/blood-types 2013

Glossary

ABO blood group
: blood-type classification based on the presence or absence of A and B glycoproteins on the erythrocyte membrane surface

agglutination
: clustering of cells into masses linked by antibodies

cross matching

blood test for identification of blood type using antibodies and small samples of blood

hemolysis

destruction (lysis) of erythrocytes and the release of their hemoglobin into circulation

hemolytic disease of the newborn (HDN)

(also, erythroblastosis fetalis) disorder causing agglutination and hemolysis in an Rh^+ fetus or newborn of an Rh^- mother

Rh blood group

blood-type classification based on the presence or absence of the antigen Rh on the erythrocyte membrane surface

universal donor

individual with type O^- blood

universal recipient

individual with type AB^+ blood

Heart Anatomy
By the end of this section, you will be able to:

- Describe the location and position of the heart within the body cavity
- Describe the internal and external anatomy of the heart
- Identify the tissue layers of the heart
- Relate the structure of the heart to its function as a pump
- Compare systemic circulation to pulmonary circulation
- Identify the veins and arteries of the coronary circulation system
- Trace the pathway of oxygenated and deoxygenated blood thorough the chambers of the heart

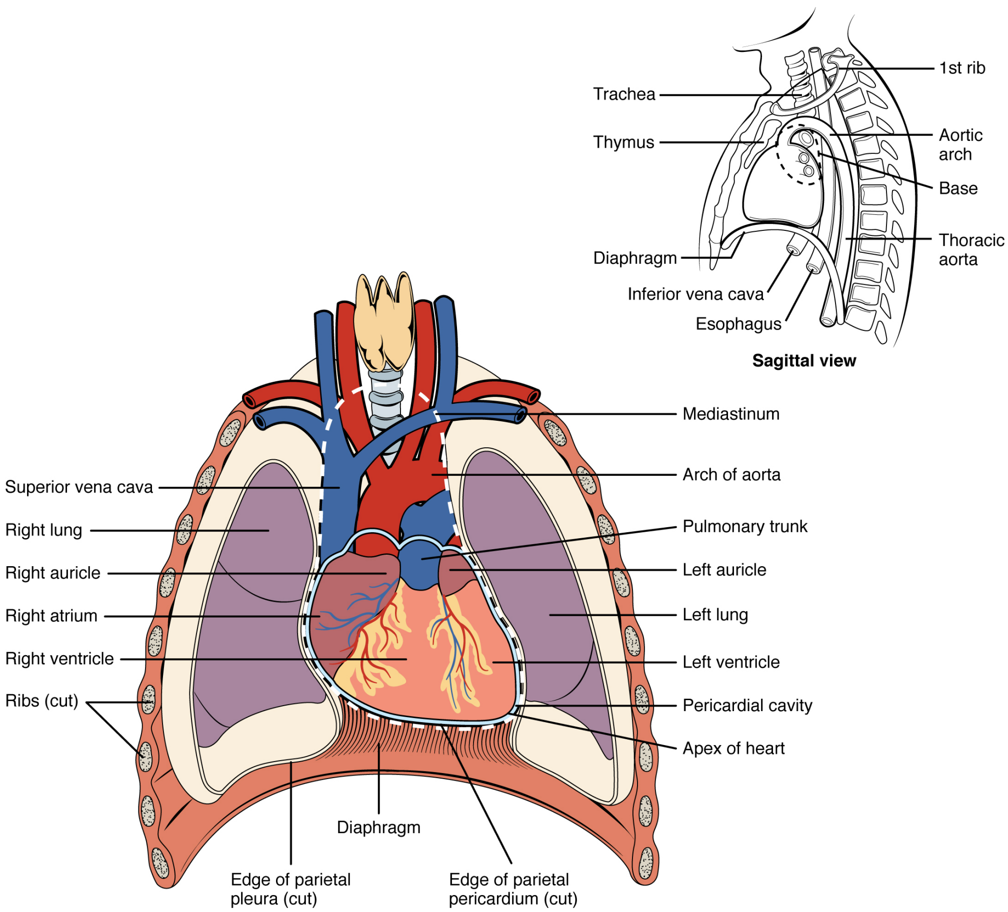
The vital importance of the heart is obvious. If one assumes an average rate of contraction of 75 contractions per minute, a human heart would contract approximately 108,000 times in one day, more than 39 million times in one year, and nearly 3 billion times during a 75-year lifespan. Each of the major pumping chambers of the heart ejects approximately 70 mL blood per contraction in a resting adult. This would be equal to 5.25 liters of fluid per minute and approximately 14,000 liters per day. Over one year, that would equal 10,000,000 liters or 2.6 million gallons of blood sent through roughly 60,000 miles of vessels. In order to understand how that happens, it is necessary to understand the anatomy and physiology of the heart.

Location of the Heart

The human heart is located within the thoracic cavity, medially between the lungs in the space known as the mediastinum. [link] shows the position of the heart within the thoracic cavity. Within the mediastinum, the heart is separated from the other mediastinal structures by a tough membrane known as the pericardium, or pericardial sac, and sits in its own space called the **pericardial cavity**. The dorsal surface of the heart lies near the bodies of the vertebrae, and its anterior surface sits deep to the sternum and costal cartilages. The great veins, the superior and inferior venae cavae, and the great arteries, the aorta and pulmonary trunk, are attached to the superior surface of the heart, called the base. The base of the heart is located at the level of the third costal cartilage, as seen in [link]. The inferior tip of the heart, the apex, lies just to the left of the sternum between

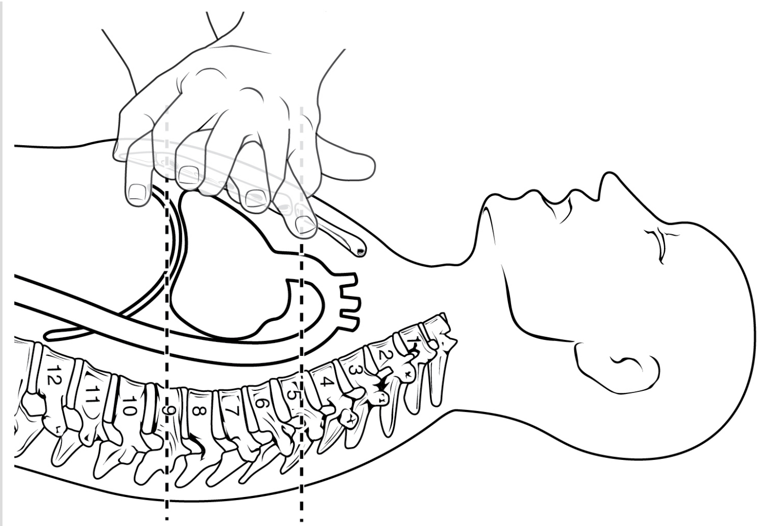
the junction of the fourth and fifth ribs near their articulation with the costal cartilages. The right side of the heart is deflected anteriorly, and the left side is deflected posteriorly. It is important to remember the position and orientation of the heart when placing a stethoscope on the chest of a patient and listening for heart sounds, and also when looking at images taken from a midsagittal perspective. The slight deviation of the apex to the left is reflected in a depression in the medial surface of the inferior lobe of the left lung, called the **cardiac notch**.

Position of the Heart in the Thorax



The heart is located within the thoracic cavity, medially between the lungs in the mediastinum. It is about the size of a fist, is broad at the top, and tapers toward the base.

Note:
Everyday Connection
CPR
The position of the heart in the torso between the vertebrae and sternum (see [link] for the position of the heart within the thorax) allows for individuals to apply an emergency technique known as cardiopulmonary resuscitation (CPR) if the heart of a patient should stop. By applying pressure with the flat portion of one hand on the sternum in the area between the line at T4 and T9 ([link]), it is possible to manually compress the blood within the heart enough to push some of the blood within it into the pulmonary and systemic circuits. This is particularly critical for the brain, as irreversible damage and death of neurons occur within minutes of loss of blood flow. Current standards call for compression of the chest at least 5 cm deep and at a rate of 100 compressions per minute, a rate equal to the beat in “Staying Alive,” recorded in 1977 by the Bee Gees. If you are unfamiliar with this song, a version is available on www.youtube.com. At this stage, the emphasis is on performing high-quality chest compressions, rather than providing artificial respiration. CPR is generally performed until the patient regains spontaneous contraction or is declared dead by an experienced healthcare professional.
When performed by untrained or overzealous individuals, CPR can result in broken ribs or a broken sternum, and can inflict additional severe damage on the patient. It is also possible, if the hands are placed too low on the sternum, to manually drive the xiphoid process into the liver, a consequence that may prove fatal for the patient. Proper training is essential. This proven life-sustaining technique is so valuable that virtually all medical personnel as well as concerned members of the public should be certified and routinely recertified in its application. CPR courses are offered at a variety of locations, including colleges, hospitals, the American Red Cross, and some commercial companies. They normally include practice of the compression technique on a mannequin.
CPR Technique



If the heart should stop, CPR can maintain the flow of blood until the heart resumes beating. By applying pressure to the sternum, the blood within the heart will be squeezed out of the heart and into the circulation. Proper positioning of the hands on the sternum to perform CPR would be between the lines at T4 and T9.

Note:

Visit the American Heart Association website to help locate a course near your home in the United States. There are also many other national and

regional heart associations that offer the same service, depending upon the location.

Shape and Size of the Heart

The shape of the heart is similar to a pinecone, rather broad at the superior surface and tapering to the apex (see [link]). A typical heart is approximately the size of your fist: 12 cm (5 in) in length, 8 cm (3.5 in) wide, and 6 cm (2.5 in) in thickness. Given the size difference between most members of the sexes, the weight of a female heart is approximately 250–300 grams (9 to 11 ounces), and the weight of a male heart is approximately 300–350 grams (11 to 12 ounces). The heart of a well-trained athlete, especially one specializing in aerobic sports, can be considerably larger than this. Cardiac muscle responds to exercise in a manner similar to that of skeletal muscle. That is, exercise results in the addition of protein myofilaments that increase the size of the individual cells without increasing their numbers, a concept called hypertrophy. Hearts of athletes can pump blood more effectively at lower rates than those of nonathletes. Enlarged hearts are not always a result of exercise; they can result from pathologies, such as **hypertrophic cardiomyopathy**. The cause of an abnormally enlarged heart muscle is unknown, but the condition is often undiagnosed and can cause sudden death in apparently otherwise healthy young people.

Chambers and Circulation through the Heart

The human heart consists of four chambers: The left side and the right side each have one **atrium** and one **ventricle**. Each of the upper chambers, the right atrium (plural = atria) and the left atrium, acts as a receiving chamber and contracts to push blood into the lower chambers, the right ventricle and the left ventricle. The ventricles serve as the primary pumping chambers of the heart, propelling blood to the lungs or to the rest of the body.

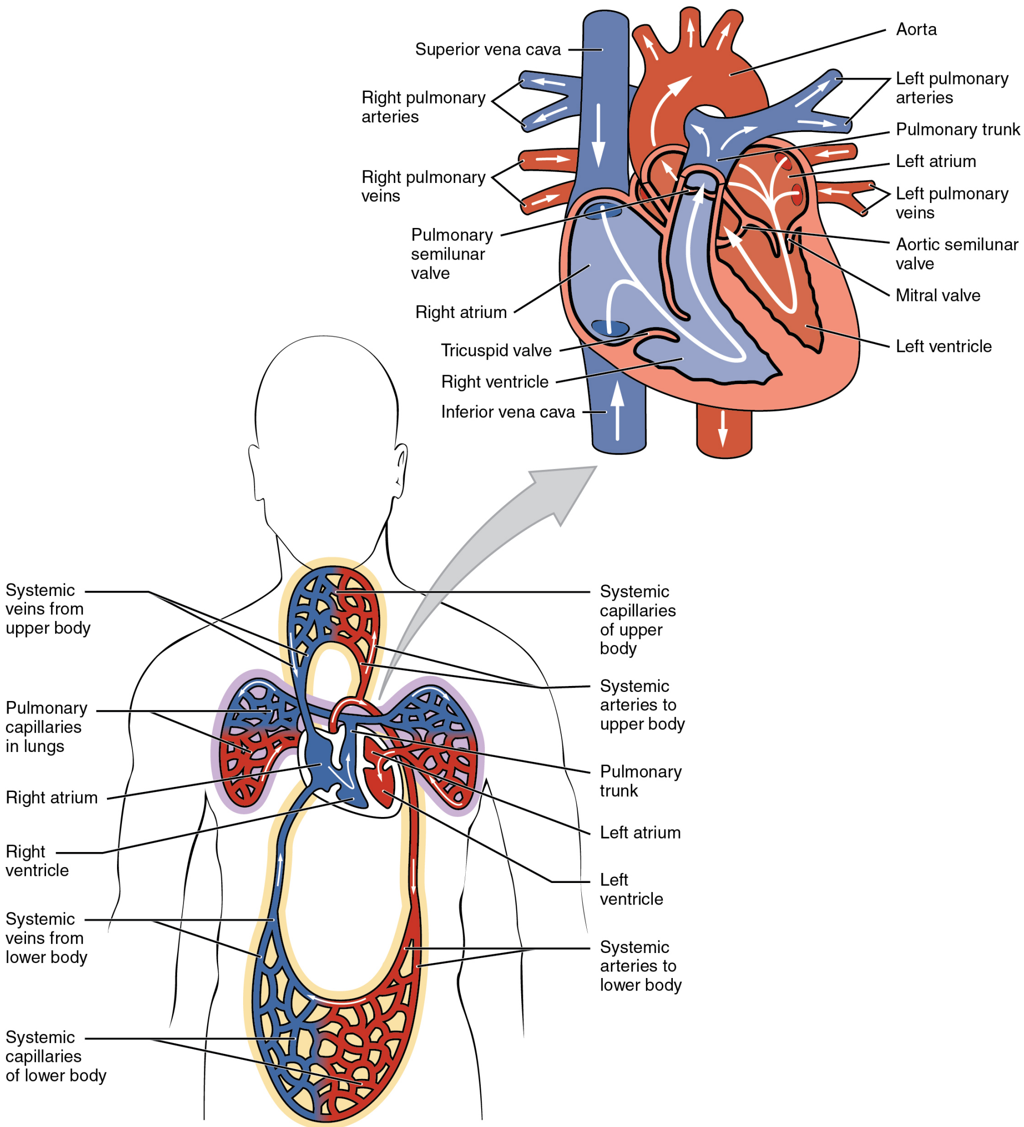
There are two distinct but linked circuits in the human circulation called the pulmonary and systemic circuits. Although both circuits transport blood and

everything it carries, we can initially view the circuits from the point of view of gases. The **pulmonary circuit** transports blood to and from the lungs, where it picks up oxygen and delivers carbon dioxide for exhalation. The **systemic circuit** transports oxygenated blood to virtually all of the tissues of the body and returns relatively deoxygenated blood and carbon dioxide to the heart to be sent back to the pulmonary circulation.

The right ventricle pumps deoxygenated blood into the **pulmonary trunk**, which leads toward the lungs and bifurcates into the left and right **pulmonary arteries**. These vessels in turn branch many times before reaching the **pulmonary capillaries**, where gas exchange occurs: Carbon dioxide exits the blood and oxygen enters. The pulmonary trunk arteries and their branches are the only arteries in the post-natal body that carry relatively deoxygenated blood. Highly oxygenated blood returning from the pulmonary capillaries in the lungs passes through a series of vessels that join together to form the **pulmonary veins**—the only post-natal veins in the body that carry highly oxygenated blood. The pulmonary veins conduct blood into the left atrium, which pumps the blood into the left ventricle, which in turn pumps oxygenated blood into the aorta and on to the many branches of the systemic circuit. Eventually, these vessels will lead to the systemic capillaries, where exchange with the tissue fluid and cells of the body occurs. In this case, oxygen and nutrients exit the systemic capillaries to be used by the cells in their metabolic processes, and carbon dioxide and waste products will enter the blood.

The blood exiting the systemic capillaries is lower in oxygen concentration than when it entered. The capillaries will ultimately unite to form venules, joining to form ever-larger veins, eventually flowing into the two major systemic veins, the **superior vena cava** and the **inferior vena cava**, which return blood to the right atrium. The blood in the superior and inferior venae cavae flows into the right atrium, which pumps blood into the right ventricle. This process of blood circulation continues as long as the individual remains alive. Understanding the flow of blood through the pulmonary and systemic circuits is critical to all health professions ([link]).

Dual System of the Human Blood Circulation



Blood flows from the right atrium to the right ventricle, where it is pumped into the pulmonary circuit. The blood in the pulmonary artery branches is low in oxygen but relatively high in carbon dioxide. Gas exchange occurs in the pulmonary capillaries (oxygen into the blood, carbon dioxide out), and blood high in oxygen and low in carbon dioxide is returned to the left atrium. From here, blood enters the left ventricle, which pumps it into the systemic circuit. Following exchange in the systemic capillaries (oxygen and nutrients out of the capillaries and carbon

dioxide and wastes in), blood returns to the right atrium and the cycle is repeated.

Membranes, Surface Features, and Layers

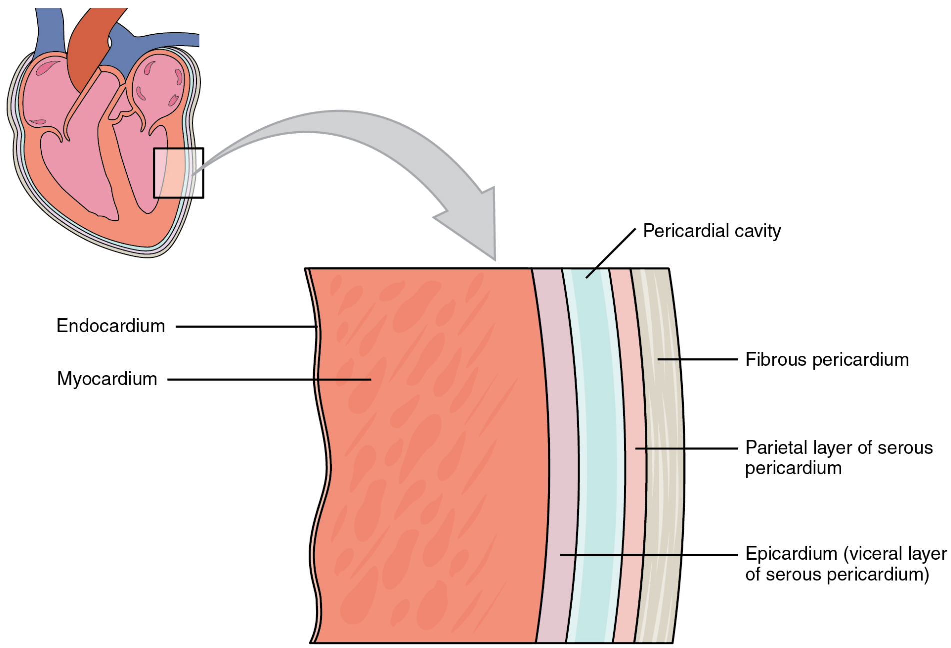
Our exploration of more in-depth heart structures begins by examining the membrane that surrounds the heart, the prominent surface features of the heart, and the layers that form the wall of the heart. Each of these components plays its own unique role in terms of function.

Membranes

The membrane that directly surrounds the heart and defines the pericardial cavity is called the **pericardium** or **pericardial sac**. It also surrounds the “roots” of the major vessels, or the areas of closest proximity to the heart. The pericardium, which literally translates as “around the heart,” consists of two distinct sublayers: the sturdy outer fibrous pericardium and the inner serous pericardium. The fibrous pericardium is made of tough, dense connective tissue that protects the heart and maintains its position in the thorax. The more delicate serous pericardium consists of two layers: the parietal pericardium, which is fused to the fibrous pericardium, and an inner visceral pericardium, or **epicardium**, which is fused to the heart and is part of the heart wall. The pericardial cavity, filled with lubricating serous fluid, lies between the epicardium and the pericardium.

In most organs within the body, visceral serous membranes such as the epicardium are microscopic. However, in the case of the heart, it is not a microscopic layer but rather a macroscopic layer, consisting of a simple squamous epithelium called a **mesothelium**, reinforced with loose, irregular, or areolar connective tissue that attaches to the pericardium. This mesothelium secretes the lubricating serous fluid that fills the pericardial cavity and reduces friction as the heart contracts. [link] illustrates the pericardial membrane and the layers of the heart.

Pericardial Membranes and Layers of the Heart Wall



The pericardial membrane that surrounds the heart consists of three layers and the pericardial cavity. The heart wall also consists of three layers. The pericardial membrane and the heart wall share the epicardium.

Note:
Disorders of the…

Heart: Cardiac Tamponade

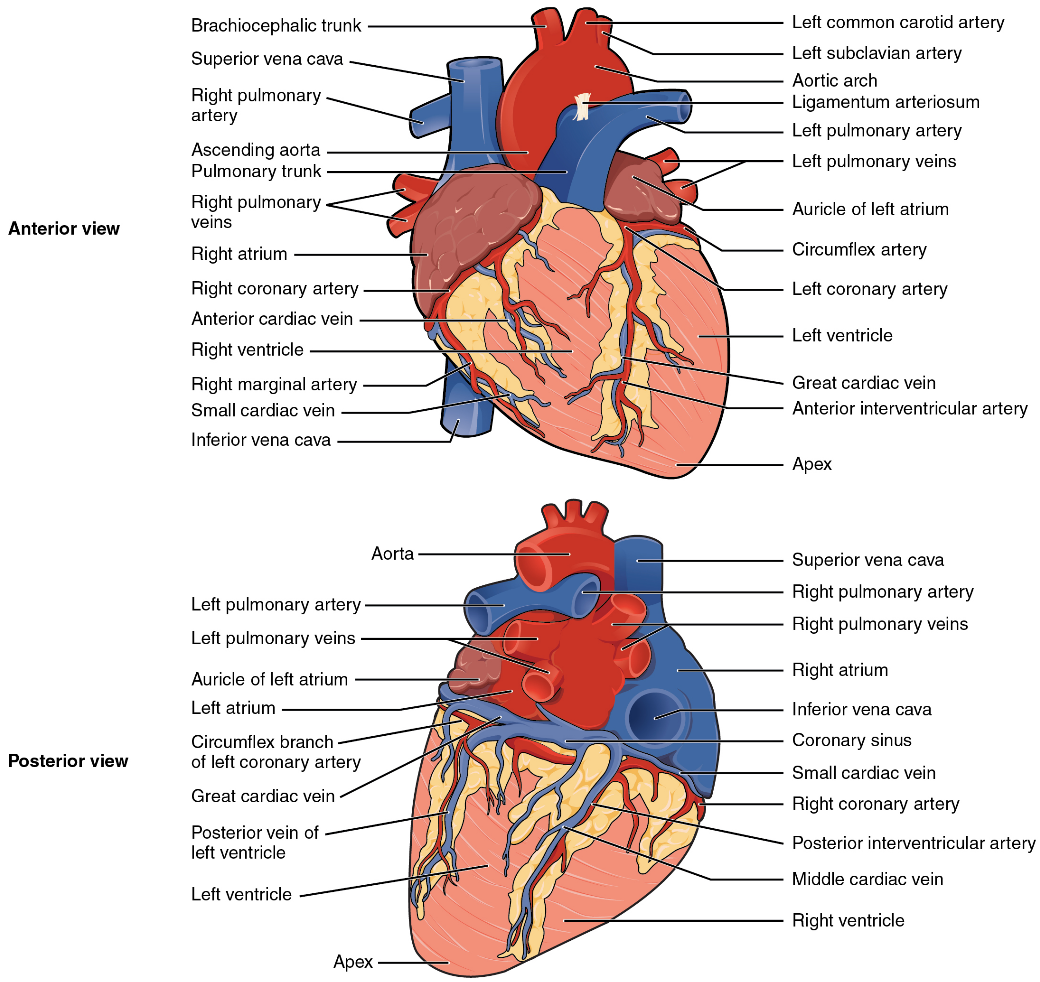
If excess fluid builds within the pericardial space, it can lead to a condition called cardiac tamponade, or pericardial tamponade. With each contraction of the heart, more fluid—in most instances, blood—accumulates within the pericardial cavity. In order to fill with blood for the next contraction, the heart must relax. However, the excess fluid in the pericardial cavity puts pressure on the heart and prevents full relaxation, so the chambers within the heart contain slightly less blood as they begin each heart cycle. Over time, less and less blood is ejected from the heart. If the fluid builds up slowly, as in hypothyroidism, the pericardial cavity may be able to expand gradually to accommodate this extra volume. Some cases of fluid in excess

of one liter within the pericardial cavity have been reported. Rapid accumulation of as little as 100 mL of fluid following trauma may trigger cardiac tamponade. Other common causes include myocardial rupture, pericarditis, cancer, or even cardiac surgery. Removal of this excess fluid requires insertion of drainage tubes into the pericardial cavity. Premature removal of these drainage tubes, for example, following cardiac surgery, or clot formation within these tubes are causes of this condition. Untreated, cardiac tamponade can lead to death.

Surface Features of the Heart

Inside the pericardium, the surface features of the heart are visible, including the four chambers. There is a superficial leaf-like extension of the atria near the superior surface of the heart, one on each side, called an **auricle**—a name that means "ear like"—because its shape resembles the external ear of a human ([link]). Auricles are relatively thin-walled structures that can fill with blood and empty into the atria or upper chambers of the heart. You may also hear them referred to as atrial appendages. Also prominent is a series of fat-filled grooves, each of which is known as a **sulcus** (plural = sulci), along the superior surfaces of the heart. Major coronary blood vessels are located in these sulci. The deep **coronary sulcus** is located between the atria and ventricles. Located between the left and right ventricles are two additional sulci that are not as deep as the coronary sulcus. The **anterior interventricular sulcus** is visible on the anterior surface of the heart, whereas the **posterior interventricular sulcus** is visible on the posterior surface of the heart. [link] illustrates anterior and posterior views of the surface of the heart.

External Anatomy of the Heart



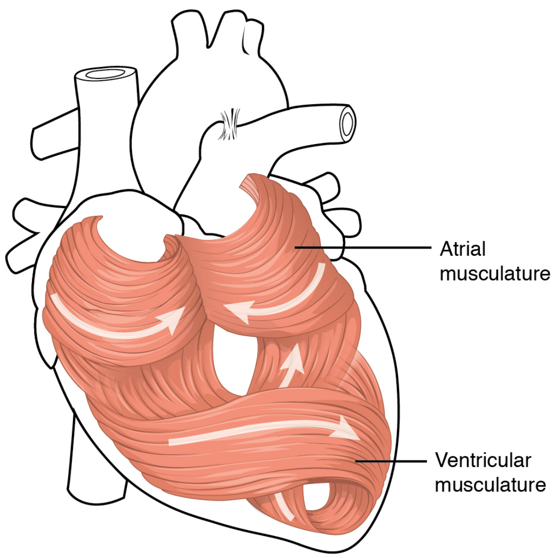
Inside the pericardium, the surface features of the heart are visible.

Layers

The wall of the heart is composed of three layers of unequal thickness. From superficial to deep, these are the epicardium, the myocardium, and the endocardium (see [link]). The outermost layer of the wall of the heart is also the innermost layer of the pericardium, the epicardium, or the visceral pericardium discussed earlier.

The middle and thickest layer is the **myocardium**, made largely of cardiac muscle cells. It is built upon a framework of collagenous fibers, plus the blood vessels that supply the myocardium and the nerve fibers that help regulate the heart. It is the contraction of the myocardium that pumps blood through the heart and into the major arteries. The muscle pattern is elegant and complex, as the muscle cells swirl and spiral around the chambers of the heart. They form a figure 8 pattern around the atria and around the bases of the great vessels. Deeper ventricular muscles also form a figure 8 around the two ventricles and proceed toward the apex. More superficial layers of ventricular muscle wrap around both ventricles. This complex swirling pattern allows the heart to pump blood more effectively than a simple linear pattern would. [link] illustrates the arrangement of muscle cells.

Heart Musculature

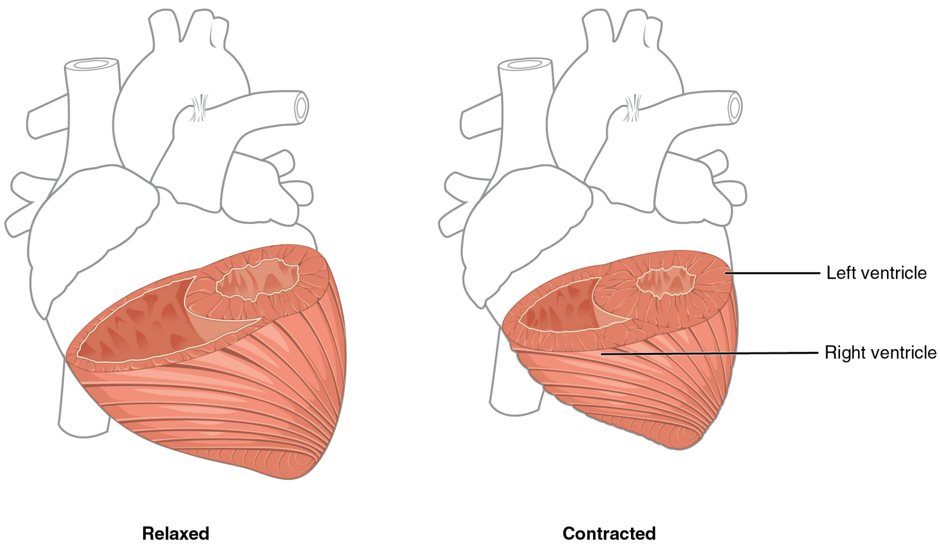


The swirling pattern of cardiac muscle tissue contributes significantly to the heart's ability to pump blood effectively.

Although the ventricles on the right and left sides pump the same amount of blood per contraction, the muscle of the left ventricle is much thicker and better developed than that of the right ventricle. In order to overcome the

high resistance required to pump blood into the long systemic circuit, the left ventricle must generate a great amount of pressure. The right ventricle does not need to generate as much pressure, since the pulmonary circuit is shorter and provides less resistance. [link] illustrates the differences in muscular thickness needed for each of the ventricles.

Differences in Ventricular Muscle Thickness



The myocardium in the left ventricle is significantly thicker than that of the right ventricle. Both ventricles pump the same amount of blood, but the left ventricle must generate a much greater pressure to overcome greater resistance in the systemic circuit. The ventricles are shown in both relaxed and contracting states. Note the differences in the relative size of the lumens, the region inside each ventricle where the blood is contained.

The innermost layer of the heart wall, the **endocardium**, is joined to the myocardium with a thin layer of connective tissue. The endocardium lines the chambers where the blood circulates and covers the heart valves. It is made of simple squamous epithelium called **endothelium**, which is continuous with the endothelial lining of the blood vessels (see [link]).

Once regarded as a simple lining layer, recent evidence indicates that the endothelium of the endocardium and the coronary capillaries may play active roles in regulating the contraction of the muscle within the myocardium. The endothelium may also regulate the growth patterns of the cardiac muscle cells throughout life, and the endothelins it secretes create an environment in the surrounding tissue fluids that regulates ionic concentrations and states of contractility. Endothelins are potent vasoconstrictors and, in a normal individual, establish a homeostatic balance with other vasoconstrictors and vasodilators.

Internal Structure of the Heart

Recall that the heart's contraction cycle follows a dual pattern of circulation—the pulmonary and systemic circuits—because of the pairs of chambers that pump blood into the circulation. In order to develop a more precise understanding of cardiac function, it is first necessary to explore the internal anatomical structures in more detail.

Septa of the Heart

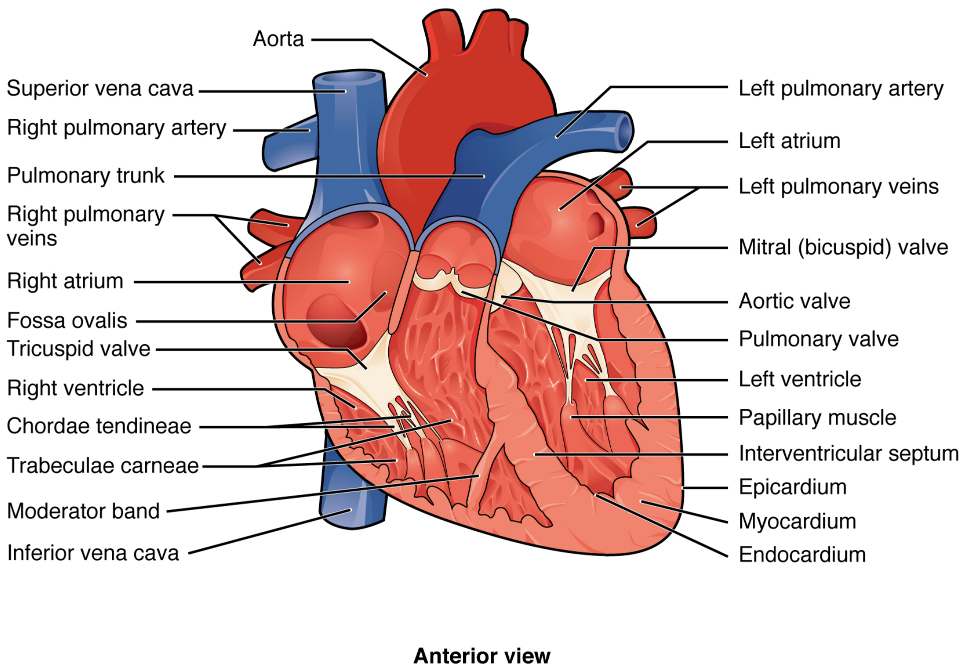
The word septum is derived from the Latin for "something that encloses;" in this case, a **septum** (plural = septa) refers to a wall or partition that divides the heart into chambers. The septa are physical extensions of the myocardium lined with endocardium. Located between the two atria is the **interatrial septum**. Normally in an adult heart, the interatrial septum bears an oval-shaped depression known as the **fossa ovalis**, a remnant of an opening in the fetal heart known as the **foramen ovale**. The foramen ovale allowed blood in the fetal heart to pass directly from the right atrium to the left atrium, allowing some blood to bypass the pulmonary circuit. Within seconds after birth, a flap of tissue known as the **septum primum** that previously acted as a valve closes the foramen ovale and establishes the typical cardiac circulation pattern.

Between the two ventricles is a second septum known as the **interventricular septum**. Unlike the interatrial septum, the interventricular

septum is normally intact after its formation during fetal development. It is substantially thicker than the interatrial septum, since the ventricles generate far greater pressure when they contract.

The septum between the atria and ventricles is known as the **atrioventricular septum**. It is marked by the presence of four openings that allow blood to move from the atria into the ventricles and from the ventricles into the pulmonary trunk and aorta. Located in each of these openings between the atria and ventricles is a **valve**, a specialized structure that ensures one-way flow of blood. The valves between the atria and ventricles are known generically as **atrioventricular valves**. The valves at the openings that lead to the pulmonary trunk and aorta are known generically as **semilunar valves**. The interventricular septum is visible in [link]. In this figure, the atrioventricular septum has been removed to better show the bicuspid and tricuspid valves; the interatrial septum is not visible, since its location is covered by the aorta and pulmonary trunk. Since these openings and valves structurally weaken the atrioventricular septum, the remaining tissue is heavily reinforced with dense connective tissue called the **cardiac skeleton**, or skeleton of the heart. It includes four rings that surround the openings between the atria and ventricles, and the openings to the pulmonary trunk and aorta, and serve as the point of attachment for the heart valves. The cardiac skeleton also provides an important boundary in the heart electrical conduction system.

Internal Structures of the Heart



This anterior view of the heart shows the four chambers, the major vessels and their early branches, as well as the valves. The presence of the pulmonary trunk and aorta covers the interatrial septum, and the atrioventricular septum is cut away to show the atrioventricular valves.

Note:

Disorders of the…

Heart: Heart Defects

One very common form of interatrial septum pathology is patent foramen ovale, which occurs when the septum primum does not close at birth, and the fossa ovalis is unable to fuse. The word patent is from the Latin root patens for “open.” It may be benign or asymptomatic, perhaps never being diagnosed, or in extreme cases, it may require surgical repair to close the opening permanently. As much as 20–25 percent of the general population may have a patent foramen ovale, but fortunately, most have the benign,

asymptomatic version. Patent foramen ovale is normally detected by auscultation of a heart murmur (an abnormal heart sound) and confirmed by imaging with an echocardiogram. Despite its prevalence in the general population, the causes of patent ovale are unknown, and there are no known risk factors. In nonlife-threatening cases, it is better to monitor the condition than to risk heart surgery to repair and seal the opening.

Coarctation of the aorta is a congenital abnormal narrowing of the aorta that is normally located at the insertion of the ligamentum arteriosum, the remnant of the fetal shunt called the ductus arteriosus. If severe, this condition drastically restricts blood flow through the primary systemic artery, which is life threatening. In some individuals, the condition may be fairly benign and not detected until later in life. Detectable symptoms in an infant include difficulty breathing, poor appetite, trouble feeding, or failure to thrive. In older individuals, symptoms include dizziness, fainting, shortness of breath, chest pain, fatigue, headache, and nosebleeds. Treatment involves surgery to resect (remove) the affected region or angioplasty to open the abnormally narrow passageway. Studies have shown that the earlier the surgery is performed, the better the chance of survival.

A patent ductus arteriosus is a congenital condition in which the ductus arteriosus fails to close. The condition may range from severe to benign. Failure of the ductus arteriosus to close results in blood flowing from the higher pressure aorta into the lower pressure pulmonary trunk. This additional fluid moving toward the lungs increases pulmonary pressure and makes respiration difficult. Symptoms include shortness of breath (dyspnea), tachycardia, enlarged heart, a widened pulse pressure, and poor weight gain in infants. Treatments include surgical closure (ligation), manual closure using platinum coils or specialized mesh inserted via the femoral artery or vein, or nonsteroidal anti-inflammatory drugs to block the synthesis of prostaglandin E2, which maintains the vessel in an open position. If untreated, the condition can result in congestive heart failure.

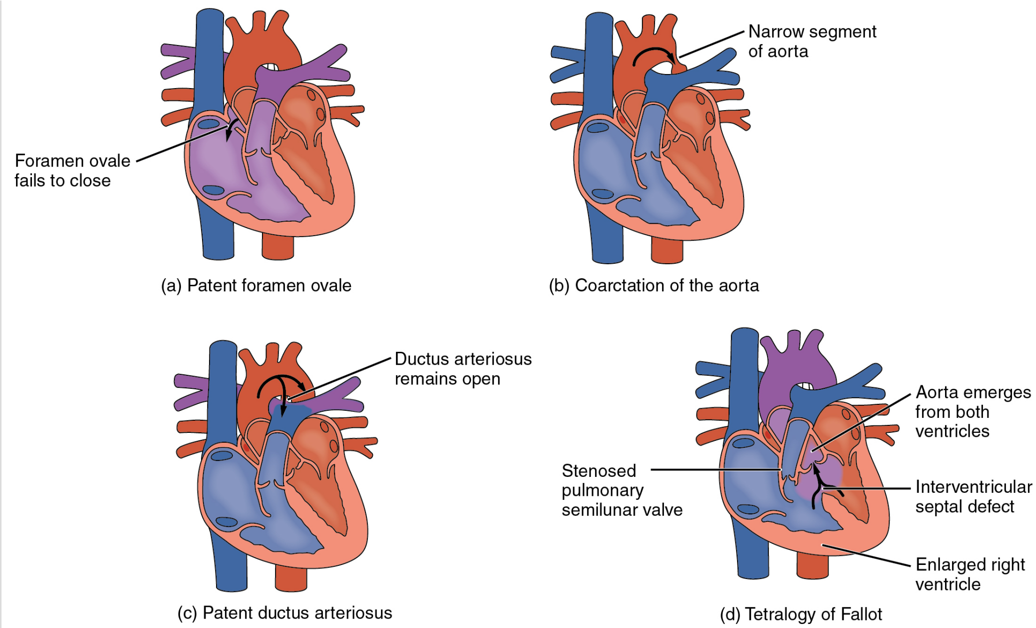
Septal defects are not uncommon in individuals and may be congenital or caused by various disease processes. Tetralogy of Fallot is a congenital condition that may also occur from exposure to unknown environmental factors; it occurs when there is an opening in the interventricular septum caused by blockage of the pulmonary trunk, normally at the pulmonary semilunar valve. This allows blood that is relatively low in oxygen from

the right ventricle to flow into the left ventricle and mix with the blood that is relatively high in oxygen. Symptoms include a distinct heart murmur, low blood oxygen percent saturation, dyspnea or difficulty in breathing, polycythemia, broadening (clubbing) of the fingers and toes, and in children, difficulty in feeding or failure to grow and develop. It is the most common cause of cyanosis following birth. The term “tetralogy” is derived from the four components of the condition, although only three may be present in an individual patient: pulmonary infundibular stenosis (rigidity of the pulmonary valve), overriding aorta (the aorta is shifted above both ventricles), ventricular septal defect (opening), and right ventricular hypertrophy (enlargement of the right ventricle). Other heart defects may also accompany this condition, which is typically confirmed by echocardiography imaging. Tetralogy of Fallot occurs in approximately 400 out of one million live births. Normal treatment involves extensive surgical repair, including the use of stents to redirect blood flow and replacement of valves and patches to repair the septal defect, but the condition has a relatively high mortality. Survival rates are currently 75 percent during the first year of life; 60 percent by 4 years of age; 30 percent by 10 years; and 5 percent by 40 years.

In the case of severe septal defects, including both tetralogy of Fallot and patent foramen ovale, failure of the heart to develop properly can lead to a condition commonly known as a “blue baby.” Regardless of normal skin pigmentation, individuals with this condition have an insufficient supply of oxygenated blood, which leads to cyanosis, a blue or purple coloration of the skin, especially when active.

Septal defects are commonly first detected through auscultation, listening to the chest using a stethoscope. In this case, instead of hearing normal heart sounds attributed to the flow of blood and closing of heart valves, unusual heart sounds may be detected. This is often followed by medical imaging to confirm or rule out a diagnosis. In many cases, treatment may not be needed. Some common congenital heart defects are illustrated in [link].

Congenital Heart Defects



(a) A patent foramen ovale defect is an abnormal opening in the interatrial septum, or more commonly, a failure of the foramen ovale to close. (b) Coarctation of the aorta is an abnormal narrowing of the aorta. (c) A patent ductus arteriosus is the failure of the ductus arteriosus to close. (d) Tetralogy of Fallot includes an abnormal opening in the interventricular septum.

Right Atrium

The right atrium serves as the receiving chamber for blood returning to the heart from the systemic circulation. The two major systemic veins, the superior and inferior venae cavae, and the large coronary vein called the **coronary sinus** that drains the heart myocardium empty into the right atrium. The superior vena cava drains blood from regions superior to the diaphragm: the head, neck, upper limbs, and the thoracic region. It empties into the superior and posterior portions of the right atrium. The inferior vena cava drains blood from areas inferior to the diaphragm: the lower limbs and abdominopelvic region of the body. It, too, empties into the

posterior portion of the atria, but inferior to the opening of the superior vena cava. Immediately superior and slightly medial to the opening of the inferior vena cava on the posterior surface of the atrium is the opening of the coronary sinus. This thin-walled vessel drains most of the coronary veins that return systemic blood from the heart. The majority of the internal heart structures discussed in this and subsequent sections are illustrated in [link].

While the bulk of the internal surface of the right atrium is smooth, the depression of the fossa ovalis is medial, and the anterior surface demonstrates prominent ridges of muscle called the **pectinate muscles**. The right auricle also has pectinate muscles. The left atrium does not have pectinate muscles except in the auricle.

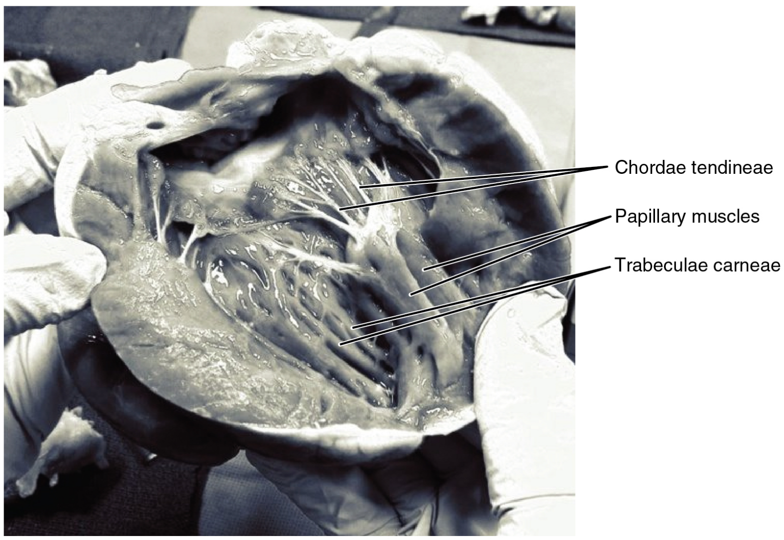
The atria receive venous blood on a nearly continuous basis, preventing venous flow from stopping while the ventricles are contracting. While most ventricular filling occurs while the atria are relaxed, they do demonstrate a contractile phase and actively pump blood into the ventricles just prior to ventricular contraction. The opening between the atrium and ventricle is guarded by the tricuspid valve.

Right Ventricle

The right ventricle receives blood from the right atrium through the tricuspid valve. Each flap of the valve is attached to strong strands of connective tissue, the **chordae tendineae**, literally “tendinous cords,” or sometimes more poetically referred to as “heart strings.” There are several chordae tendineae associated with each of the flaps. They are composed of approximately 80 percent collagenous fibers with the remainder consisting of elastic fibers and endothelium. They connect each of the flaps to a **papillary muscle** that extends from the inferior ventricular surface. There are three papillary muscles in the right ventricle, called the anterior, posterior, and septal muscles, which correspond to the three sections of the valves.

When the myocardium of the ventricle contracts, pressure within the ventricular chamber rises. Blood, like any fluid, flows from higher pressure to lower pressure areas, in this case, toward the pulmonary trunk and the atrium. To prevent any potential backflow, the papillary muscles also contract, generating tension on the chordae tendineae. This prevents the flaps of the valves from being forced into the atria and regurgitation of the blood back into the atria during ventricular contraction. [link] shows papillary muscles and chordae tendineae attached to the tricuspid valve.

Chordae Tendineae and Papillary Muscles



In this frontal section, you can see papillary muscles attached to the tricuspid valve on the right as well as the mitral valve on the left via chordae tendineae. (credit: modification of work by “PV KS”/flickr.com)

The walls of the ventricle are lined with **trabeculae carneae**, ridges of cardiac muscle covered by endocardium. In addition to these muscular ridges, a band of cardiac muscle, also covered by endocardium, known as the **moderator band** (see [link]) reinforces the thin walls of the right ventricle and plays a crucial role in cardiac conduction. It arises from the

inferior portion of the interventricular septum and crosses the interior space of the right ventricle to connect with the inferior papillary muscle.

When the right ventricle contracts, it ejects blood into the pulmonary trunk, which branches into the left and right pulmonary arteries that carry it to each lung. The superior surface of the right ventricle begins to taper as it approaches the pulmonary trunk. At the base of the pulmonary trunk is the pulmonary semilunar valve that prevents backflow from the pulmonary trunk.

Left Atrium

After exchange of gases in the pulmonary capillaries, blood returns to the left atrium high in oxygen via one of the four pulmonary veins. While the left atrium does not contain pectinate muscles, it does have an auricle that includes these pectinate ridges. Blood flows nearly continuously from the pulmonary veins back into the atrium, which acts as the receiving chamber, and from here through an opening into the left ventricle. Most blood flows passively into the heart while both the atria and ventricles are relaxed, but toward the end of the ventricular relaxation period, the left atrium will contract, pumping blood into the ventricle. This atrial contraction accounts for approximately 20 percent of ventricular filling. The opening between the left atrium and ventricle is guarded by the mitral valve.

Left Ventricle

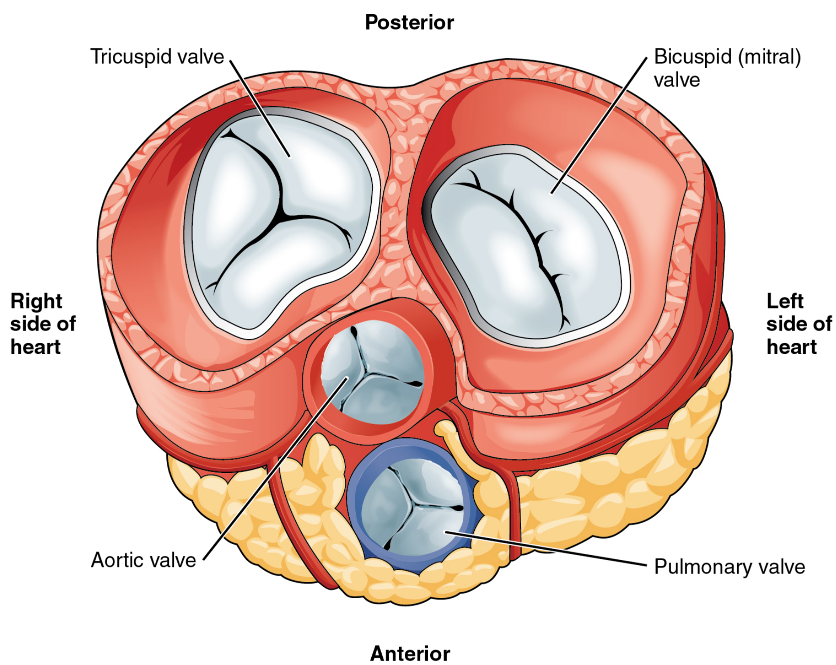
Recall that, although both sides of the heart will pump the same amount of blood, the muscular layer is much thicker in the left ventricle compared to the right (see [link]). Like the right ventricle, the left also has trabeculae carneae, but there is no moderator band. The mitral valve is connected to papillary muscles via chordae tendineae. There are two papillary muscles on the left—the anterior and posterior—as opposed to three on the right.

The left ventricle is the major pumping chamber for the systemic circuit; it ejects blood into the aorta through the aortic semilunar valve.

Heart Valve Structure and Function

A transverse section through the heart slightly above the level of the atrioventricular septum reveals all four heart valves along the same plane ([link]). The valves ensure unidirectional blood flow through the heart. Between the right atrium and the right ventricle is the **right atrioventricular valve**, or **tricuspid valve**. It typically consists of three flaps, or leaflets, made of endocardium reinforced with additional connective tissue. The flaps are connected by chordae tendineae to the papillary muscles, which control the opening and closing of the valves.

Heart Valves



With the atria and major vessels removed, all four valves are clearly visible, although it is difficult to distinguish the three separate cusps of the tricuspid valve.

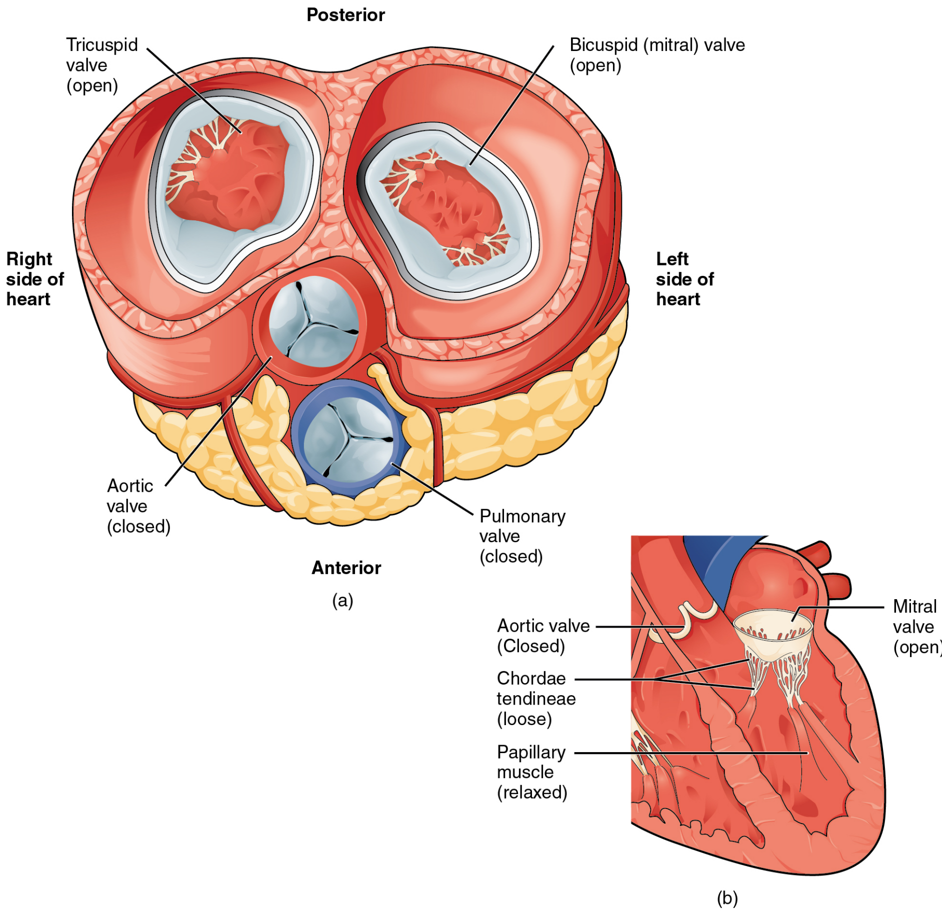
Emerging from the right ventricle at the base of the pulmonary trunk is the pulmonary semilunar valve, or the **pulmonary valve**; it is also known as the pulmonic valve or the right semilunar valve. The pulmonary valve is comprised of three small flaps of endothelium reinforced with connective tissue. When the ventricle relaxes, the pressure differential causes blood to flow back into the ventricle from the pulmonary trunk. This flow of blood fills the pocket-like flaps of the pulmonary valve, causing the valve to close and producing an audible sound. Unlike the atrioventricular valves, there are no papillary muscles or chordae tendineae associated with the pulmonary valve.

Located at the opening between the left atrium and left ventricle is the **mitral valve**, also called the **bicuspid valve** or the **left atrioventricular valve**. Structurally, this valve consists of two cusps, known as the anterior medial cusp and the posterior medial cusp, compared to the three cusps of the tricuspid valve. In a clinical setting, the valve is referred to as the mitral valve, rather than the bicuspid valve. The two cusps of the mitral valve are attached by chordae tendineae to two papillary muscles that project from the wall of the ventricle.

At the base of the aorta is the aortic semilunar valve, or the **aortic valve**, which prevents backflow from the aorta. It normally is composed of three flaps. When the ventricle relaxes and blood attempts to flow back into the ventricle from the aorta, blood will fill the cusps of the valve, causing it to close and producing an audible sound.

In [link]**a**, the two atrioventricular valves are open and the two semilunar valves are closed. This occurs when both atria and ventricles are relaxed and when the atria contract to pump blood into the ventricles. [link]**b** shows a frontal view. Although only the left side of the heart is illustrated, the process is virtually identical on the right.

Blood Flow from the Left Atrium to the Left Ventricle

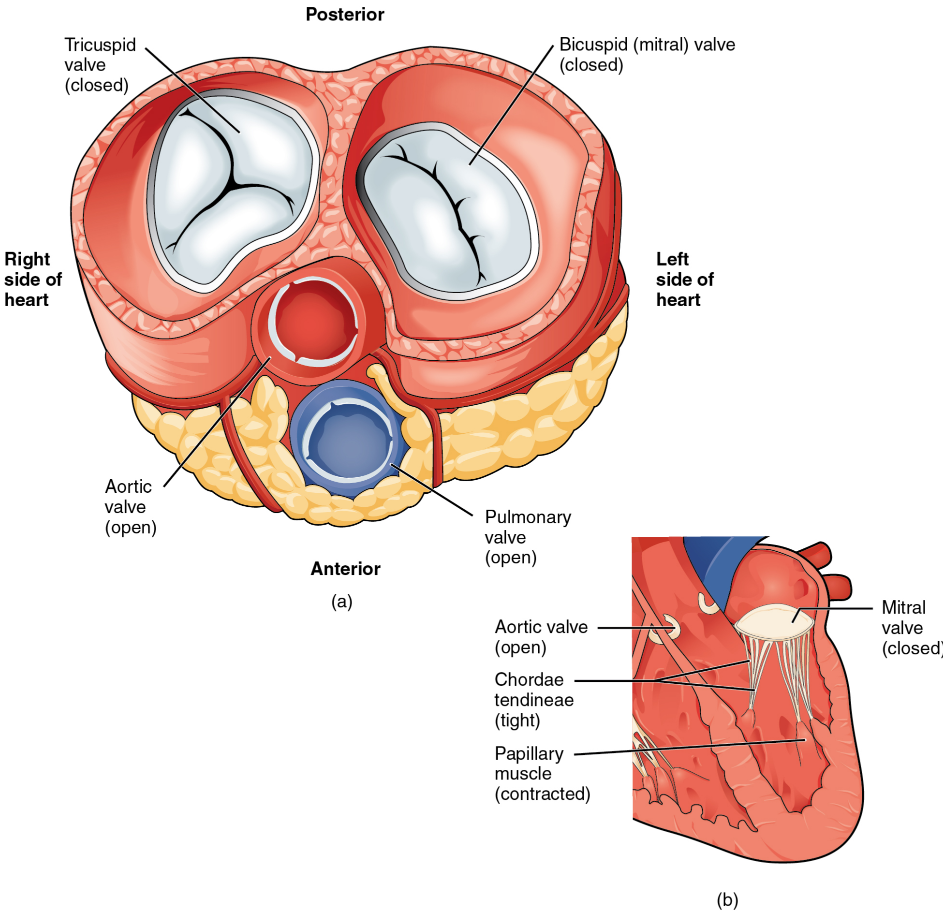


(a) A transverse section through the heart illustrates the four heart valves. The two atrioventricular valves are open; the two semilunar valves are closed. The atria and vessels have been removed. (b) A frontal section through the heart illustrates blood flow through the mitral valve. When the mitral valve is open, it allows blood to move from the left atrium to the left ventricle. The aortic semilunar valve is closed to prevent backflow of blood from the aorta to the left ventricle.

[link]**a** shows the atrioventricular valves closed while the two semilunar valves are open. This occurs when the ventricles contract to eject blood into the pulmonary trunk and aorta. Closure of the two atrioventricular valves

prevents blood from being forced back into the atria. This stage can be seen from a frontal view in [link]**b**.

Blood Flow from the Left Ventricle into the Great Vessels



(a) A transverse section through the heart illustrates the four heart valves during ventricular contraction. The two atrioventricular valves are closed, but the two semilunar valves are open. The atria and vessels have been removed. (b) A frontal view shows the closed mitral (bicuspid) valve that prevents backflow of blood into the left atrium. The aortic semilunar valve is open to allow blood to be ejected into the aorta.

When the ventricles begin to contract, pressure within the ventricles rises and blood flows toward the area of lowest pressure, which is initially in the

atria. This backflow causes the cusps of the tricuspid and mitral (bicuspid) valves to close. These valves are tied down to the papillary muscles by chordae tendineae. During the relaxation phase of the cardiac cycle, the papillary muscles are also relaxed and the tension on the chordae tendineae is slight (see [link]**b**). However, as the myocardium of the ventricle contracts, so do the papillary muscles. This creates tension on the chordae tendineae (see [link]**b**), helping to hold the cusps of the atrioventricular valves in place and preventing them from being blown back into the atria.

The aortic and pulmonary semilunar valves lack the chordae tendineae and papillary muscles associated with the atrioventricular valves. Instead, they consist of pocket-like folds of endocardium reinforced with additional connective tissue. When the ventricles relax and the change in pressure forces the blood toward the ventricles, the blood presses against these cusps and seals the openings.

Note:

Visit this site to observe an echocardiogram of actual heart valves opening and closing. Although much of the heart has been “removed” from this gif loop so the chordae tendineae are not visible, why is their presence more critical for the atrioventricular valves (tricuspid and mitral) than the semilunar (aortic and pulmonary) valves?

Note:
Disorders of the…
Heart Valves

When heart valves do not function properly, they are often described as incompetent and result in valvular heart disease, which can range from benign to lethal. Some of these conditions are congenital, that is, the individual was born with the defect, whereas others may be attributed to disease processes or trauma. Some malfunctions are treated with medications, others require surgery, and still others may be mild enough that the condition is merely monitored since treatment might trigger more serious consequences.

Valvular disorders are often caused by carditis, or inflammation of the heart. One common trigger for this inflammation is rheumatic fever, or scarlet fever, an autoimmune response to the presence of a bacterium, *Streptococcus pyogenes*, normally a disease of childhood.

While any of the heart valves may be involved in valve disorders, mitral regurgitation is the most common, detected in approximately 2 percent of the population, and the pulmonary semilunar valve is the least frequently involved. When a valve malfunctions, the flow of blood to a region will often be disrupted. The resulting inadequate flow of blood to this region will be described in general terms as an insufficiency. The specific type of insufficiency is named for the valve involved: aortic insufficiency, mitral insufficiency, tricuspid insufficiency, or pulmonary insufficiency.

If one of the cusps of the valve is forced backward by the force of the blood, the condition is referred to as a prolapsed valve. Prolapse may occur if the chordae tendineae are damaged or broken, causing the closure mechanism to fail. The failure of the valve to close properly disrupts the normal one-way flow of blood and results in regurgitation, when the blood flows backward from its normal path. Using a stethoscope, the disruption to the normal flow of blood produces a heart murmur.

Stenosis is a condition in which the heart valves become rigid and may calcify over time. The loss of flexibility of the valve interferes with normal function and may cause the heart to work harder to propel blood through the valve, which eventually weakens the heart. Aortic stenosis affects approximately 2 percent of the population over 65 years of age, and the percentage increases to approximately 4 percent in individuals over 85 years. Occasionally, one or more of the chordae tendineae will tear or the papillary muscle itself may die as a component of a myocardial infarction (heart attack). In this case, the patient’s condition will deteriorate

dramatically and rapidly, and immediate surgical intervention may be required.
Auscultation, or listening to a patient's heart sounds, is one of the most useful diagnostic tools, since it is proven, safe, and inexpensive. The term auscultation is derived from the Latin for "to listen," and the technique has been used for diagnostic purposes as far back as the ancient Egyptians. Valve and septal disorders will trigger abnormal heart sounds. If a valvular disorder is detected or suspected, a test called an echocardiogram, or simply an "echo," may be ordered. Echocardiograms are sonograms of the heart and can help in the diagnosis of valve disorders as well as a wide variety of heart pathologies.

Note:

Visit this site for a free download, including excellent animations and audio of heart sounds.

Note:
Career Connection
Cardiologist
Cardiologists are medical doctors that specialize in the diagnosis and treatment of diseases of the heart. After completing 4 years of medical school, cardiologists complete a three-year residency in internal medicine followed by an additional three or more years in cardiology. Following this 10-year period of medical training and clinical experience, they qualify for a rigorous two-day examination administered by the Board of Internal Medicine that tests their academic training and clinical abilities, including

diagnostics and treatment. After successful completion of this examination, a physician becomes a board-certified cardiologist. Some board-certified cardiologists may be invited to become a Fellow of the American College of Cardiology (FACC). This professional recognition is awarded to outstanding physicians based upon merit, including outstanding credentials, achievements, and community contributions to cardiovascular medicine.

Note:

Visit this site to learn more about cardiologists.

Note:
Career Connection
Cardiovascular Technologist/Technician
Cardiovascular technologists/technicians are trained professionals who perform a variety of imaging techniques, such as sonograms or echocardiograms, used by physicians to diagnose and treat diseases of the heart. Nearly all of these positions require an associate degree, and these technicians earn a median salary of $49,410 as of May 2010, according to the U.S. Bureau of Labor Statistics. Growth within the field is fast, projected at 29 percent from 2010 to 2020.
There is a considerable overlap and complementary skills between cardiac technicians and vascular technicians, and so the term cardiovascular technician is often used. Special certifications within the field require documenting appropriate experience and completing additional and often expensive certification examinations. These subspecialties include

Certified Rhythm Analysis Technician (CRAT), Certified Cardiographic Technician (CCT), Registered Congenital Cardiac Sonographer (RCCS), Registered Cardiac Electrophysiology Specialist (RCES), Registered Cardiovascular Invasive Specialist (RCIS), Registered Cardiac Sonographer (RCS), Registered Vascular Specialist (RVS), and Registered Phlebology Sonographer (RPhS).

Note:

Visit this site for more information on cardiovascular technologists/technicians.

Coronary Circulation

You will recall that the heart is a remarkable pump composed largely of cardiac muscle cells that are incredibly active throughout life. Like all other cells, a **cardiomyocyte** requires a reliable supply of oxygen and nutrients, and a way to remove wastes, so it needs a dedicated, complex, and extensive coronary circulation. And because of the critical and nearly ceaseless activity of the heart throughout life, this need for a blood supply is even greater than for a typical cell. However, coronary circulation is not continuous; rather, it cycles, reaching a peak when the heart muscle is relaxed and nearly ceasing while it is contracting.

Coronary Arteries

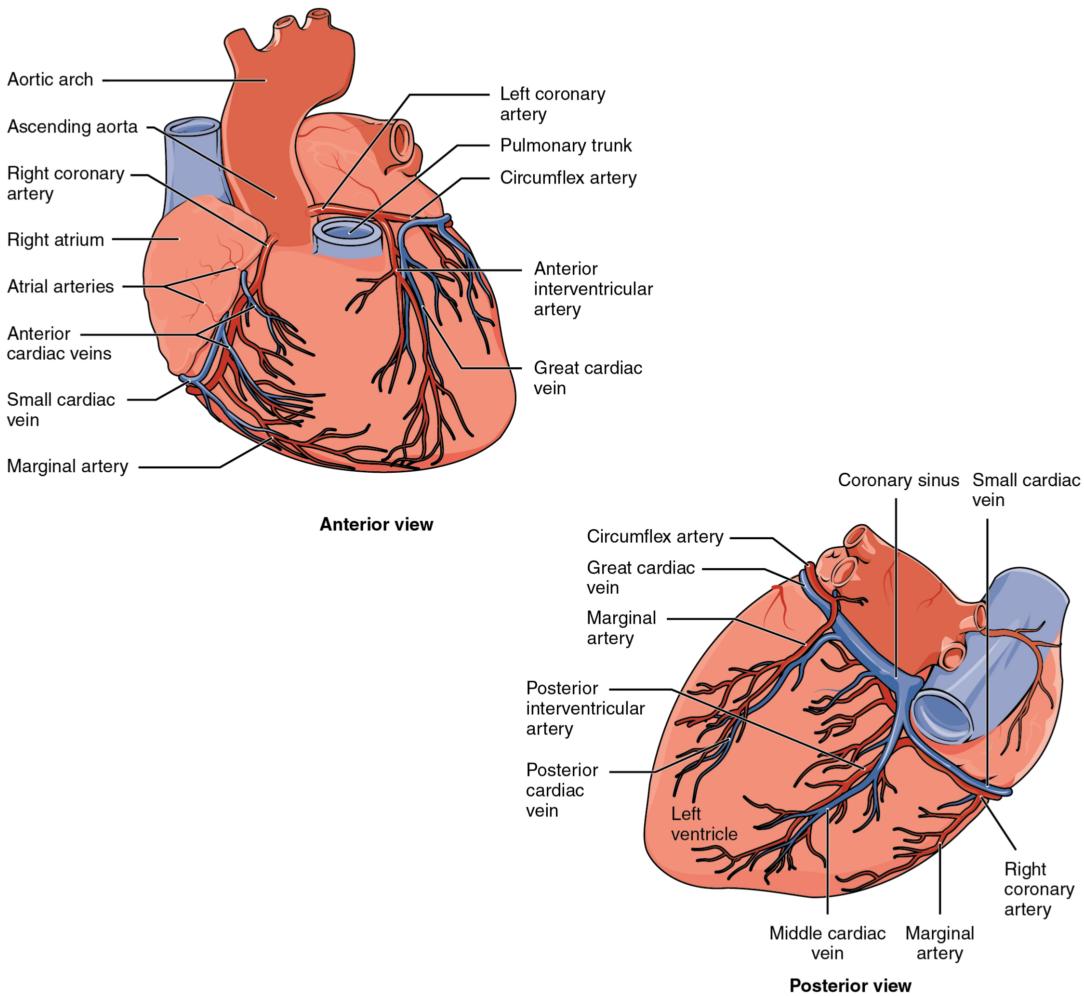
Coronary arteries supply blood to the myocardium and other components of the heart. The first portion of the aorta after it arises from the left ventricle gives rise to the coronary arteries. There are three dilations in the wall of the aorta just superior to the aortic semilunar valve. Two of these, the left posterior aortic sinus and anterior aortic sinus, give rise to the left and right coronary arteries, respectively. The third sinus, the right posterior aortic sinus, typically does not give rise to a vessel. Coronary vessel branches that remain on the surface of the artery and follow the sulci are called **epicardial coronary arteries**.

The left coronary artery distributes blood to the left side of the heart, the left atrium and ventricle, and the interventricular septum. The **circumflex artery** arises from the left coronary artery and follows the coronary sulcus to the left. Eventually, it will fuse with the small branches of the right coronary artery. The larger **anterior interventricular artery**, also known as the left anterior descending artery (LAD), is the second major branch arising from the left coronary artery. It follows the anterior interventricular sulcus around the pulmonary trunk. Along the way it gives rise to numerous smaller branches that interconnect with the branches of the posterior interventricular artery, forming anastomoses. An **anastomosis** is an area where vessels unite to form interconnections that normally allow blood to circulate to a region even if there may be partial blockage in another branch. The anastomoses in the heart are very small. Therefore, this ability is somewhat restricted in the heart so a coronary artery blockage often results in death of the cells (myocardial infarction) supplied by the particular vessel.

The right coronary artery proceeds along the coronary sulcus and distributes blood to the right atrium, portions of both ventricles, and the heart conduction system. Normally, one or more marginal arteries arise from the right coronary artery inferior to the right atrium. The **marginal arteries** supply blood to the superficial portions of the right ventricle. On the posterior surface of the heart, the right coronary artery gives rise to the **posterior interventricular artery**, also known as the posterior descending artery. It runs along the posterior portion of the interventricular sulcus toward the apex of the heart, giving rise to branches that supply the interventricular septum and portions of both ventricles. [link] presents

views of the coronary circulation from both the anterior and posterior views.

Coronary Circulation



The anterior view of the heart shows the prominent coronary surface vessels. The posterior view of the heart shows the prominent coronary surface vessels.

Note:

Diseases of the…

Heart: Myocardial Infarction

Myocardial infarction (MI) is the formal term for what is commonly referred to as a heart attack. It normally results from a lack of blood flow (ischemia) and oxygen (hypoxia) to a region of the heart, resulting in death of the cardiac muscle cells. An MI often occurs when a coronary artery is blocked by the buildup of atherosclerotic plaque consisting of lipids, cholesterol and fatty acids, and white blood cells, primarily macrophages. It can also occur when a portion of an unstable atherosclerotic plaque travels through the coronary arterial system and lodges in one of the smaller vessels. The resulting blockage restricts the flow of blood and oxygen to the myocardium and causes death of the tissue. MIs may be triggered by excessive exercise, in which the partially occluded artery is no longer able to pump sufficient quantities of blood, or severe stress, which may induce spasm of the smooth muscle in the walls of the vessel.

In the case of acute MI, there is often sudden pain beneath the sternum (retrosternal pain) called angina pectoris, often radiating down the left arm in males but not in female patients. Until this anomaly between the sexes was discovered, many female patients suffering MIs were misdiagnosed and sent home. In addition, patients typically present with difficulty breathing and shortness of breath (dyspnea), irregular heartbeat (palpations), nausea and vomiting, sweating (diaphoresis), anxiety, and fainting (syncope), although not all of these symptoms may be present. Many of the symptoms are shared with other medical conditions, including anxiety attacks and simple indigestion, so differential diagnosis is critical. It is estimated that between 22 and 64 percent of MIs present without any symptoms.

An MI can be confirmed by examining the patient’s ECG, which frequently reveals alterations in the ST and Q components. Some classification schemes of MI are referred to as ST-elevated MI (STEMI) and non-elevated MI (non-STEMI). In addition, echocardiography or cardiac magnetic resonance imaging may be employed. Common blood tests indicating an MI include elevated levels of creatine kinase MB (an enzyme that catalyzes the conversion of creatine to phosphocreatine, consuming ATP) and cardiac troponin (the regulatory protein for muscle contraction), both of which are released by damaged cardiac muscle cells. Immediate treatments for MI are essential and include administering supplemental oxygen, aspirin that helps to break up clots, and nitroglycerine administered sublingually (under the tongue) to facilitate its

absorption. Despite its unquestioned success in treatments and use since the 1880s, the mechanism of nitroglycerine is still incompletely understood but is believed to involve the release of nitric oxide, a known vasodilator, and endothelium-derived releasing factor, which also relaxes the smooth muscle in the tunica media of coronary vessels. Longer-term treatments include injections of thrombolytic agents such as streptokinase that dissolve the clot, the anticoagulant heparin, balloon angioplasty and stents to open blocked vessels, and bypass surgery to allow blood to pass around the site of blockage. If the damage is extensive, coronary replacement with a donor heart or coronary assist device, a sophisticated mechanical device that supplements the pumping activity of the heart, may be employed. Despite the attention, development of artificial hearts to augment the severely limited supply of heart donors has proven less than satisfactory but will likely improve in the future.

MIs may trigger cardiac arrest, but the two are not synonymous. Important risk factors for MI include cardiovascular disease, age, smoking, high blood levels of the low-density lipoprotein (LDL, often referred to as “bad” cholesterol), low levels of high-density lipoprotein (HDL, or “good” cholesterol), hypertension, diabetes mellitus, obesity, lack of physical exercise, chronic kidney disease, excessive alcohol consumption, and use of illegal drugs.

Coronary Veins

Coronary veins drain the heart and generally parallel the large surface arteries (see [link]). The **great cardiac vein** can be seen initially on the surface of the heart following the interventricular sulcus, but it eventually flows along the coronary sulcus into the coronary sinus on the posterior surface. The great cardiac vein initially parallels the anterior interventricular artery and drains the areas supplied by this vessel. It receives several major branches, including the posterior cardiac vein, the middle cardiac vein, and the small cardiac vein. The **posterior cardiac vein** parallels and drains the areas supplied by the marginal artery branch of the circumflex artery. The **middle cardiac vein** parallels and drains the areas supplied by the posterior interventricular artery. The **small cardiac vein**

parallels the right coronary artery and drains the blood from the posterior surfaces of the right atrium and ventricle. The coronary sinus is a large, thin-walled vein on the posterior surface of the heart lying within the atrioventricular sulcus and emptying directly into the right atrium. The **anterior cardiac veins** parallel the small cardiac arteries and drain the anterior surface of the right ventricle. Unlike these other cardiac veins, it bypasses the coronary sinus and drains directly into the right atrium.

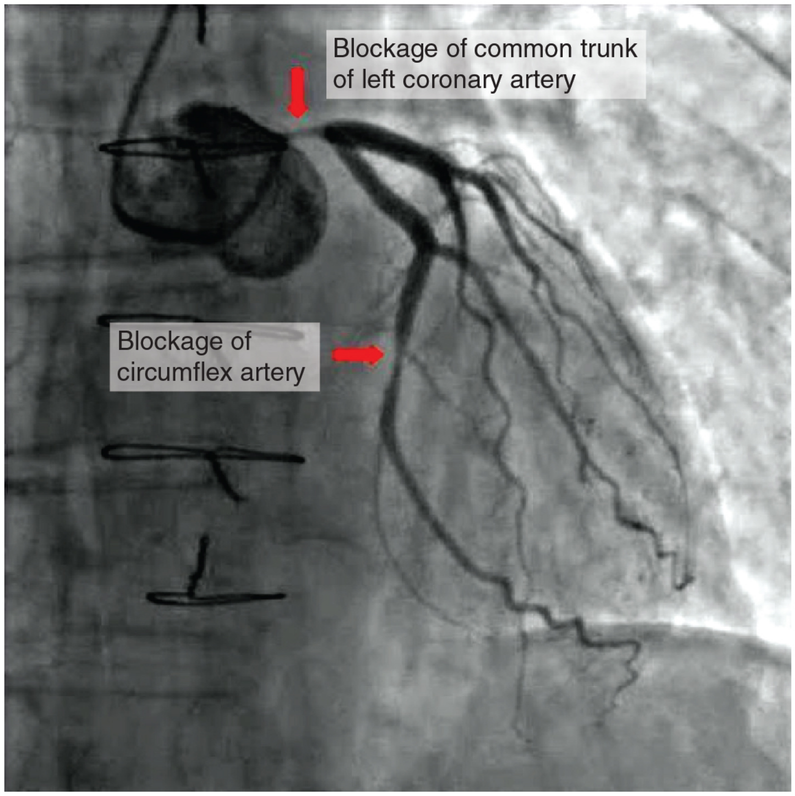
Note:

Diseases of the…

Heart: Coronary Artery Disease

Coronary artery disease is the leading cause of death worldwide. It occurs when the buildup of plaque—a fatty material including cholesterol, connective tissue, white blood cells, and some smooth muscle cells—within the walls of the arteries obstructs the flow of blood and decreases the flexibility or compliance of the vessels. This condition is called atherosclerosis, a hardening of the arteries that involves the accumulation of plaque. As the coronary blood vessels become occluded, the flow of blood to the tissues will be restricted, a condition called ischemia that causes the cells to receive insufficient amounts of oxygen, called hypoxia. [link] shows the blockage of coronary arteries highlighted by the injection of dye. Some individuals with coronary artery disease report pain radiating from the chest called angina pectoris, but others remain asymptomatic. If untreated, coronary artery disease can lead to MI or a heart attack.

Atherosclerotic Coronary Arteries



In this coronary angiogram (X-ray), the dye makes visible two occluded coronary arteries. Such blockages can lead to decreased blood flow (ischemia) and insufficient oxygen (hypoxia) delivered to the cardiac tissues. If uncorrected, this can lead to cardiac muscle death (myocardial infarction).

The disease progresses slowly and often begins in children and can be seen as fatty “streaks” in the vessels. It then gradually progresses throughout life. Well-documented risk factors include smoking, family history, hypertension, obesity, diabetes, high alcohol consumption, lack of exercise, stress, and hyperlipidemia or high circulating levels of lipids in the blood. Treatments may include medication, changes to diet and exercise, angioplasty with a balloon catheter, insertion of a stent, or coronary bypass procedure.

Angioplasty is a procedure in which the occlusion is mechanically widened with a balloon. A specialized catheter with an expandable tip is inserted into a superficial vessel, normally in the leg, and then directed to the site of the occlusion. At this point, the balloon is inflated to compress the plaque material and to open the vessel to increase blood flow. Then, the balloon is deflated and retracted. A stent consisting of a specialized mesh is typically inserted at the site of occlusion to reinforce the weakened and damaged walls. Stent insertions have been routine in cardiology for more than 40 years.

Coronary bypass surgery may also be performed. This surgical procedure grafts a replacement vessel obtained from another, less vital portion of the body to bypass the occluded area. This procedure is clearly effective in treating patients experiencing a MI, but overall does not increase longevity. Nor does it seem advisable in patients with stable although diminished cardiac capacity since frequently loss of mental acuity occurs following the procedure. Long-term changes to behavior, emphasizing diet and exercise plus a medicine regime tailored to lower blood pressure, lower cholesterol and lipids, and reduce clotting are equally as effective.

Chapter Review

The heart resides within the pericardial sac and is located in the mediastinal space within the thoracic cavity. The pericardial sac consists of two fused layers: an outer fibrous capsule and an inner parietal pericardium lined with a serous membrane. Between the pericardial sac and the heart is the pericardial cavity, which is filled with lubricating serous fluid. The walls of the heart are composed of an outer epicardium, a thick myocardium, and an inner lining layer of endocardium. The human heart consists of a pair of atria, which receive blood and pump it into a pair of ventricles, which pump blood into the vessels. The right atrium receives systemic blood relatively low in oxygen and pumps it into the right ventricle, which pumps it into the pulmonary circuit. Exchange of oxygen and carbon dioxide occurs in the lungs, and blood high in oxygen returns to the left atrium, which pumps blood into the left ventricle, which in turn pumps blood into the aorta and the remainder of the systemic circuit. The septa are the partitions that

separate the chambers of the heart. They include the interatrial septum, the interventricular septum, and the atrioventricular septum. Two of these openings are guarded by the atrioventricular valves, the right tricuspid valve and the left mitral valve, which prevent the backflow of blood. Each is attached to chordae tendineae that extend to the papillary muscles, which are extensions of the myocardium, to prevent the valves from being blown back into the atria. The pulmonary valve is located at the base of the pulmonary trunk, and the left semilunar valve is located at the base of the aorta. The right and left coronary arteries are the first to branch off the aorta and arise from two of the three sinuses located near the base of the aorta and are generally located in the sulci. Cardiac veins parallel the small cardiac arteries and generally drain into the coronary sinus.

Interactive Link Questions

Exercise:

Problem:

Visit this site to observe an echocardiogram of actual heart valves opening and closing. Although much of the heart has been "removed" from this gif loop so the chordae tendineae are not visible, why is their presence more critical for the atrioventricular valves (tricuspid and mitral) than the semilunar (aortic and pulmonary) valves?

Solution:

The pressure gradient between the atria and the ventricles is much greater than that between the ventricles and the pulmonary trunk and aorta. Without the presence of the chordae tendineae and papillary muscles, the valves would be blown back (prolapsed) into the atria and blood would regurgitate.

Review Questions

Exercise:

Problem:

Which of the following is not important in preventing backflow of blood?

a. chordae tendineae
b. papillary muscles
c. AV valves
d. endocardium

Solution:

D

Exercise:

Problem: Which valve separates the left atrium from the left ventricle?

a. mitral
b. tricuspid
c. pulmonary
d. aortic

Solution:

A

Exercise:

Problem:

Which of the following lists the valves in the order through which the blood flows from the vena cava through the heart?

a. tricuspid, pulmonary semilunar, bicuspid, aortic semilunar
b. mitral, pulmonary semilunar, bicuspid, aortic semilunar
c. aortic semilunar, pulmonary semilunar, tricuspid, bicuspid

d. bicuspid, aortic semilunar, tricuspid, pulmonary semilunar

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Solution:

A

Exercise:

Problem:

Which chamber initially receives blood from the systemic circuit?

a. left atrium
b. left ventricle
c. right atrium
d. right ventricle

Solution:

C

Exercise:

Problem:

The _________ layer secretes chemicals that help to regulate ionic environments and strength of contraction and serve as powerful vasoconstrictors.

a. pericardial sac
b. endocardium
c. myocardium
d. epicardium

Solution:

B

Exercise:

Problem: The myocardium would be the thickest in the ________.

a. left atrium
b. left ventricle
c. right atrium
d. right ventricle

Solution:

B

Exercise:

Problem: In which septum is it normal to find openings in the adult?

a. interatrial septum
b. interventricular septum
c. atrioventricular septum
d. all of the above

Solution:

C

Critical Thinking Questions

Exercise:

Problem:

Describe how the valves keep the blood moving in one direction.

Solution:

When the ventricles contract and pressure begins to rise in the ventricles, there is an initial tendency for blood to flow back (regurgitate) to the atria. However, the papillary muscles also contract, placing tension on the chordae tendineae and holding the atrioventricular valves (tricuspid and mitral) in place to prevent the valves from prolapsing and being forced back into the atria. The semilunar valves (pulmonary and aortic) lack chordae tendineae and papillary muscles, but do not face the same pressure gradients as do the atrioventricular valves. As the ventricles relax and pressure drops within the ventricles, there is a tendency for the blood to flow backward. However, the valves, consisting of reinforced endothelium and connective tissue, fill with blood and seal off the opening preventing the return of blood.

Exercise:

Problem:

Why is the pressure in the pulmonary circulation lower than in the systemic circulation?

Solution:

The pulmonary circuit consists of blood flowing to and from the lungs, whereas the systemic circuit carries blood to and from the entire body. The systemic circuit is far more extensive, consisting of far more vessels and offers much greater resistance to the flow of blood, so the heart must generate a higher pressure to overcome this resistance. This can be seen in the thickness of the myocardium in the ventricles.

Glossary

anastomosis
: (plural = anastomoses) area where vessels unite to allow blood to circulate even if there may be partial blockage in another branch

anterior cardiac veins

vessels that parallel the small cardiac arteries and drain the anterior surface of the right ventricle; bypass the coronary sinus and drain directly into the right atrium

anterior interventricular artery
: (also, left anterior descending artery or LAD) major branch of the left coronary artery that follows the anterior interventricular sulcus

anterior interventricular sulcus
: sulcus located between the left and right ventricles on the anterior surface of the heart

aortic valve
: (also, aortic semilunar valve) valve located at the base of the aorta

atrioventricular septum
: cardiac septum located between the atria and ventricles; atrioventricular valves are located here

atrioventricular valves
: one-way valves located between the atria and ventricles; the valve on the right is called the tricuspid valve, and the one on the left is the mitral or bicuspid valve

atrium
: (plural = atria) upper or receiving chamber of the heart that pumps blood into the lower chambers just prior to their contraction; the right atrium receives blood from the systemic circuit that flows into the right ventricle; the left atrium receives blood from the pulmonary circuit that flows into the left ventricle

auricle
: extension of an atrium visible on the superior surface of the heart

bicuspid valve
: (also, mitral valve or left atrioventricular valve) valve located between the left atrium and ventricle; consists of two flaps of tissue

cardiac notch
: depression in the medial surface of the inferior lobe of the left lung where the apex of the heart is located

cardiac skeleton
: (also, skeleton of the heart) reinforced connective tissue located within the atrioventricular septum; includes four rings that surround the openings between the atria and ventricles, and the openings to the pulmonary trunk and aorta; the point of attachment for the heart valves

cardiomyocyte
: muscle cell of the heart

chordae tendineae
: string-like extensions of tough connective tissue that extend from the flaps of the atrioventricular valves to the papillary muscles

circumflex artery
: branch of the left coronary artery that follows coronary sulcus

coronary arteries
: branches of the ascending aorta that supply blood to the heart; the left coronary artery feeds the left side of the heart, the left atrium and ventricle, and the interventricular septum; the right coronary artery feeds the right atrium, portions of both ventricles, and the heart conduction system

coronary sinus
: large, thin-walled vein on the posterior surface of the heart that lies within the atrioventricular sulcus and drains the heart myocardium directly into the right atrium

coronary sulcus
: sulcus that marks the boundary between the atria and ventricles

coronary veins
: vessels that drain the heart and generally parallel the large surface arteries

endocardium
: innermost layer of the heart lining the heart chambers and heart valves; composed of endothelium reinforced with a thin layer of connective tissue that binds to the myocardium

endothelium
: layer of smooth, simple squamous epithelium that lines the endocardium and blood vessels

epicardial coronary arteries
: surface arteries of the heart that generally follow the sulci

epicardium
: innermost layer of the serous pericardium and the outermost layer of the heart wall

foramen ovale
: opening in the fetal heart that allows blood to flow directly from the right atrium to the left atrium, bypassing the fetal pulmonary circuit

fossa ovalis
: oval-shaped depression in the interatrial septum that marks the former location of the foramen ovale

great cardiac vein
: vessel that follows the interventricular sulcus on the anterior surface of the heart and flows along the coronary sulcus into the coronary sinus on the posterior surface; parallels the anterior interventricular artery and drains the areas supplied by this vessel

hypertrophic cardiomyopathy
: pathological enlargement of the heart, generally for no known reason

inferior vena cava
: large systemic vein that returns blood to the heart from the inferior portion of the body

interatrial septum

cardiac septum located between the two atria; contains the fossa ovalis after birth

interventricular septum
: cardiac septum located between the two ventricles

left atrioventricular valve
: (also, mitral valve or bicuspid valve) valve located between the left atrium and ventricle; consists of two flaps of tissue

marginal arteries
: branches of the right coronary artery that supply blood to the superficial portions of the right ventricle

mesothelium
: simple squamous epithelial portion of serous membranes, such as the superficial portion of the epicardium (the visceral pericardium) and the deepest portion of the pericardium (the parietal pericardium)

middle cardiac vein
: vessel that parallels and drains the areas supplied by the posterior interventricular artery; drains into the great cardiac vein

mitral valve
: (also, left atrioventricular valve or bicuspid valve) valve located between the left atrium and ventricle; consists of two flaps of tissue

moderator band
: band of myocardium covered by endocardium that arises from the inferior portion of the interventricular septum in the right ventricle and crosses to the anterior papillary muscle; contains conductile fibers that carry electrical signals followed by contraction of the heart

myocardium
: thickest layer of the heart composed of cardiac muscle cells built upon a framework of primarily collagenous fibers and blood vessels that supply it and the nervous fibers that help to regulate it

papillary muscle
: extension of the myocardium in the ventricles to which the chordae tendineae attach

pectinate muscles
: muscular ridges seen on the anterior surface of the right atrium

pericardial cavity
: cavity surrounding the heart filled with a lubricating serous fluid that reduces friction as the heart contracts

pericardial sac
: (also, pericardium) membrane that separates the heart from other mediastinal structures; consists of two distinct, fused sublayers: the fibrous pericardium and the parietal pericardium

pericardium
: (also, pericardial sac) membrane that separates the heart from other mediastinal structures; consists of two distinct, fused sublayers: the fibrous pericardium and the parietal pericardium

posterior cardiac vein
: vessel that parallels and drains the areas supplied by the marginal artery branch of the circumflex artery; drains into the great cardiac vein

posterior interventricular artery
: (also, posterior descending artery) branch of the right coronary artery that runs along the posterior portion of the interventricular sulcus toward the apex of the heart and gives rise to branches that supply the interventricular septum and portions of both ventricles

posterior interventricular sulcus
: sulcus located between the left and right ventricles on the anterior surface of the heart

pulmonary arteries

left and right branches of the pulmonary trunk that carry deoxygenated blood from the heart to each of the lungs

pulmonary capillaries
: capillaries surrounding the alveoli of the lungs where gas exchange occurs: carbon dioxide exits the blood and oxygen enters

pulmonary circuit
: blood flow to and from the lungs

pulmonary trunk
: large arterial vessel that carries blood ejected from the right ventricle; divides into the left and right pulmonary arteries

pulmonary valve
: (also, pulmonary semilunar valve, the pulmonic valve, or the right semilunar valve) valve at the base of the pulmonary trunk that prevents backflow of blood into the right ventricle; consists of three flaps

pulmonary veins
: veins that carry highly oxygenated blood into the left atrium, which pumps the blood into the left ventricle, which in turn pumps oxygenated blood into the aorta and to the many branches of the systemic circuit

right atrioventricular valve
: (also, tricuspid valve) valve located between the right atrium and ventricle; consists of three flaps of tissue

semilunar valves
: valves located at the base of the pulmonary trunk and at the base of the aorta

septum
: (plural = septa) walls or partitions that divide the heart into chambers

septum primum

flap of tissue in the fetus that covers the foramen ovale within a few seconds after birth

small cardiac vein
parallels the right coronary artery and drains blood from the posterior surfaces of the right atrium and ventricle; drains into the great cardiac vein

sulcus
(plural = sulci) fat-filled groove visible on the surface of the heart; coronary vessels are also located in these areas

superior vena cava
large systemic vein that returns blood to the heart from the superior portion of the body

systemic circuit
blood flow to and from virtually all of the tissues of the body

trabeculae carneae
ridges of muscle covered by endocardium located in the ventricles

tricuspid valve
term used most often in clinical settings for the right atrioventricular valve

valve
in the cardiovascular system, a specialized structure located within the heart or vessels that ensures one-way flow of blood

ventricle
one of the primary pumping chambers of the heart located in the lower portion of the heart; the left ventricle is the major pumping chamber on the lower left side of the heart that ejects blood into the systemic circuit via the aorta and receives blood from the left atrium; the right ventricle is the major pumping chamber on the lower right side of the heart that ejects blood into the pulmonary circuit via the pulmonary trunk and receives blood from the right atrium

Cardiac Muscle and Electrical Activity
By the end of this section, you will be able to:

- Describe the structure of cardiac muscle
- Identify and describe the components of the conducting system that distributes electrical impulses through the heart
- Compare the effect of ion movement on membrane potential of cardiac conductive and contractile cells
- Relate characteristics of an electrocardiogram to events in the cardiac cycle
- Identify blocks that can interrupt the cardiac cycle

Recall that cardiac muscle shares a few characteristics with both skeletal muscle and smooth muscle, but it has some unique properties of its own. Not the least of these exceptional properties is its ability to initiate an electrical potential at a fixed rate that spreads rapidly from cell to cell to trigger the contractile mechanism. This property is known as **autorhythmicity**. Neither smooth nor skeletal muscle can do this. Even though cardiac muscle has autorhythmicity, heart rate is modulated by the endocrine and nervous systems.

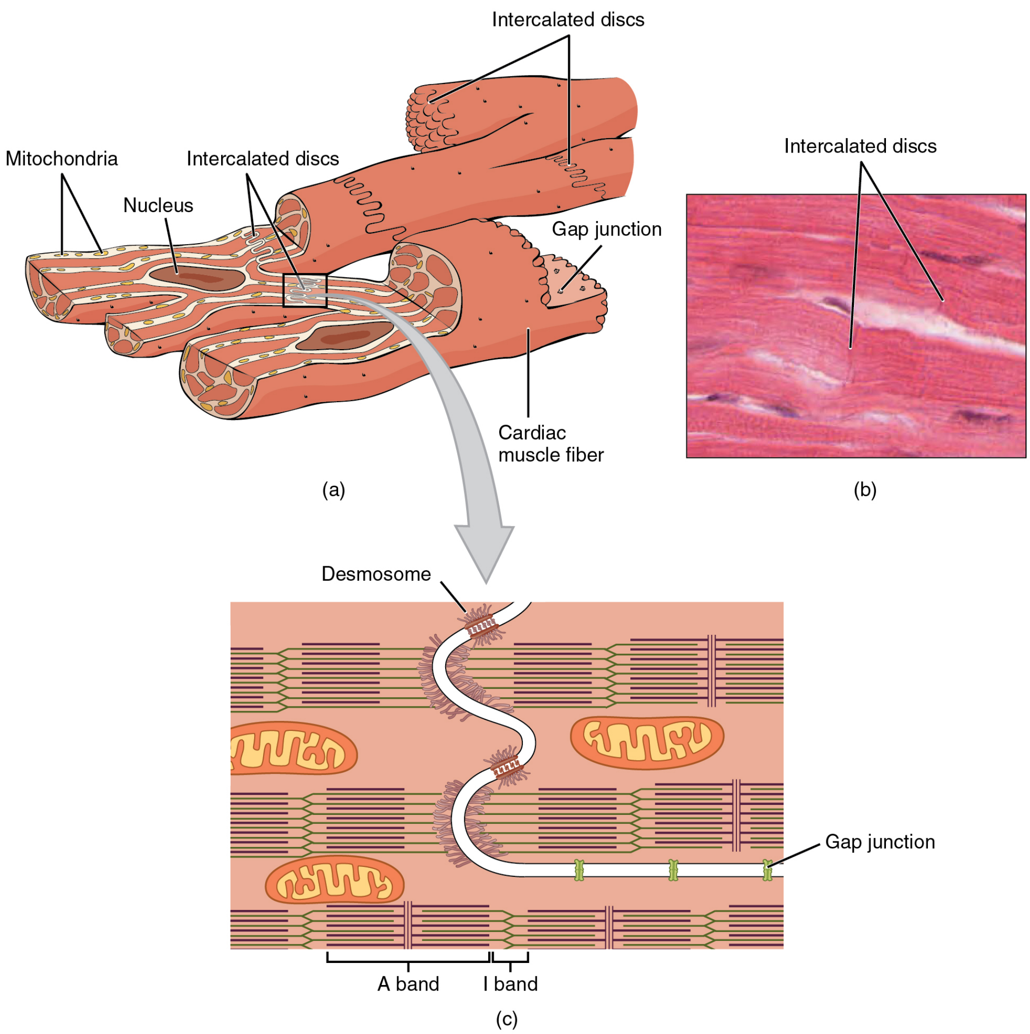
There are two major types of cardiac muscle cells: myocardial contractile cells and myocardial conducting cells. The **myocardial contractile cells** constitute the bulk (99 percent) of the cells in the atria and ventricles. Contractile cells conduct impulses and are responsible for contractions that pump blood through the body. The **myocardial conducting cells** (1 percent of the cells) form the conduction system of the heart. Except for Purkinje cells, they are generally much smaller than the contractile cells and have few of the myofibrils or filaments needed for contraction. Their function is similar in many respects to neurons, although they are specialized muscle cells. Myocardial conduction cells initiate and propagate the action potential (the electrical impulse) that travels throughout the heart and triggers the contractions that propel the blood.

Structure of Cardiac Muscle

Compared to the giant cylinders of skeletal muscle, cardiac muscle cells, or cardiomyocytes, are considerably shorter with much smaller diameters. Cardiac muscle also demonstrates striations, the alternating pattern of dark A bands and light I bands attributed to the precise arrangement of the myofilaments and fibrils that are organized in sarcomeres along the length of the cell ([link]**a**). These contractile elements are virtually identical to skeletal muscle. T (transverse) tubules penetrate from the surface plasma membrane, the sarcolemma, to the interior of the cell, allowing the electrical impulse to reach the interior. The T tubules are only found at the Z discs, whereas in skeletal muscle, they are found at the junction of the A and I bands. Therefore, there are one-half as many T tubules in cardiac muscle as in skeletal muscle. In addition, the sarcoplasmic reticulum stores few calcium ions, so most of the calcium ions must come from outside the cells. The result is a slower onset of contraction. Mitochondria are plentiful, providing energy for the contractions of the heart. Typically, cardiomyocytes have a single, central nucleus, but two or more nuclei may be found in some cells.

Cardiac muscle cells branch freely. A junction between two adjoining cells is marked by a critical structure called an **intercalated disc**, which helps support the synchronized contraction of the muscle ([link]**b**). The sarcolemmas from adjacent cells bind together at the intercalated discs. They consist of desmosomes, specialized linking proteoglycans, tight junctions, and large numbers of gap junctions that allow the passage of ions between the cells and help to synchronize the contraction ([link]**c**). Intercellular connective tissue also helps to bind the cells together. The importance of strongly binding these cells together is necessitated by the forces exerted by contraction.

Cardiac Muscle



(a) Cardiac muscle cells have myofibrils composed of myofilaments arranged in sarcomeres, T tubules to transmit the impulse from the sarcolemma to the interior of the cell, numerous mitochondria for energy, and intercalated discs that are found at the junction of different cardiac muscle cells. (b) A photomicrograph of cardiac muscle cells shows the nuclei and intercalated discs. (c) An intercalated disc connects cardiac muscle cells and consists of desmosomes and gap junctions. LM × 1600. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

Cardiac muscle undergoes aerobic respiration patterns, primarily metabolizing lipids and carbohydrates. Myoglobin, lipids, and glycogen are all stored within the cytoplasm. Cardiac muscle cells undergo twitch-type contractions with long refractory periods followed by brief relaxation periods. The relaxation is essential so the heart can fill with blood for the next cycle. The refractory period is very long to prevent the possibility of tetany, a condition in which muscle remains involuntarily contracted. In the heart, tetany is not compatible with life, since it would prevent the heart from pumping blood.

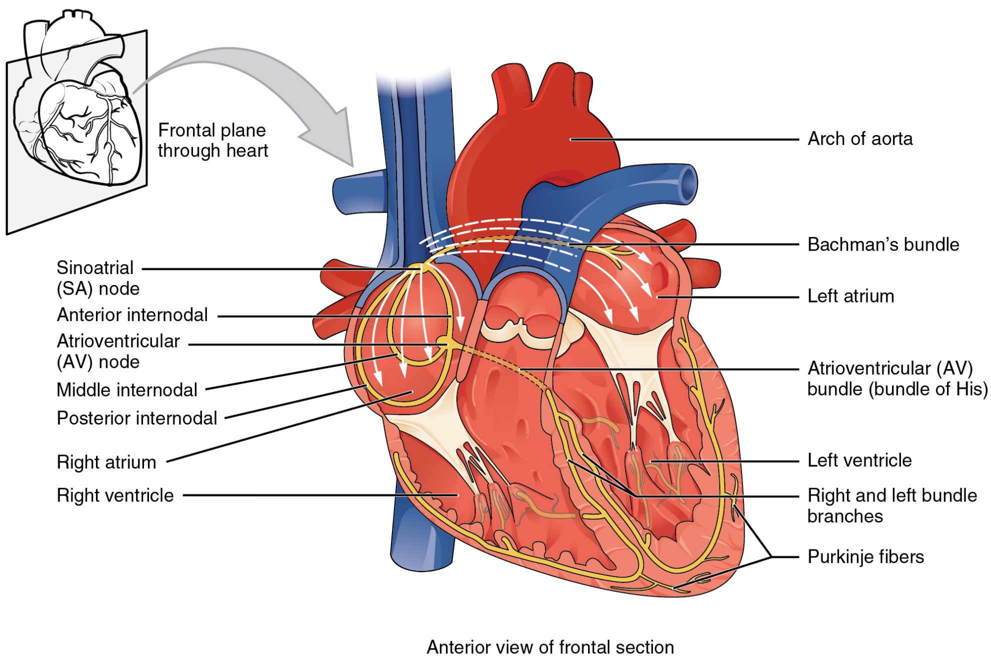
Note:
Everyday Connection
Repair and Replacement
Damaged cardiac muscle cells have extremely limited abilities to repair themselves or to replace dead cells via mitosis. Recent evidence indicates that at least some stem cells remain within the heart that continue to divide and at least potentially replace these dead cells. However, newly formed or repaired cells are rarely as functional as the original cells, and cardiac function is reduced. In the event of a heart attack or MI, dead cells are often replaced by patches of scar tissue. Autopsies performed on individuals who had successfully received heart transplants show some proliferation of original cells. If researchers can unlock the mechanism that generates new cells and restore full mitotic capabilities to heart muscle, the prognosis for heart attack survivors will be greatly enhanced. To date, myocardial cells produced within the patient (*in situ*) by cardiac stem cells seem to be nonfunctional, although those grown in Petri dishes (*in vitro*) do beat. Perhaps soon this mystery will be solved, and new advances in treatment will be commonplace.

Conduction System of the Heart

If embryonic heart cells are separated into a Petri dish and kept alive, each is capable of generating its own electrical impulse followed by contraction. When two independently beating embryonic cardiac muscle cells are placed

together, the cell with the higher inherent rate sets the pace, and the impulse spreads from the faster to the slower cell to trigger a contraction. As more cells are joined together, the fastest cell continues to assume control of the rate. A fully developed adult heart maintains the capability of generating its own electrical impulse, triggered by the fastest cells, as part of the cardiac conduction system. The components of the cardiac conduction system include the sinoatrial node, the atrioventricular node, the atrioventricular bundle, the atrioventricular bundle branches, and the Purkinje cells ([link]).

Conduction System of the Heart



Specialized conducting components of the heart include the sinoatrial node, the internodal pathways, the atrioventricular node, the atrioventricular bundle, the right and left bundle branches, and the Purkinje fibers.

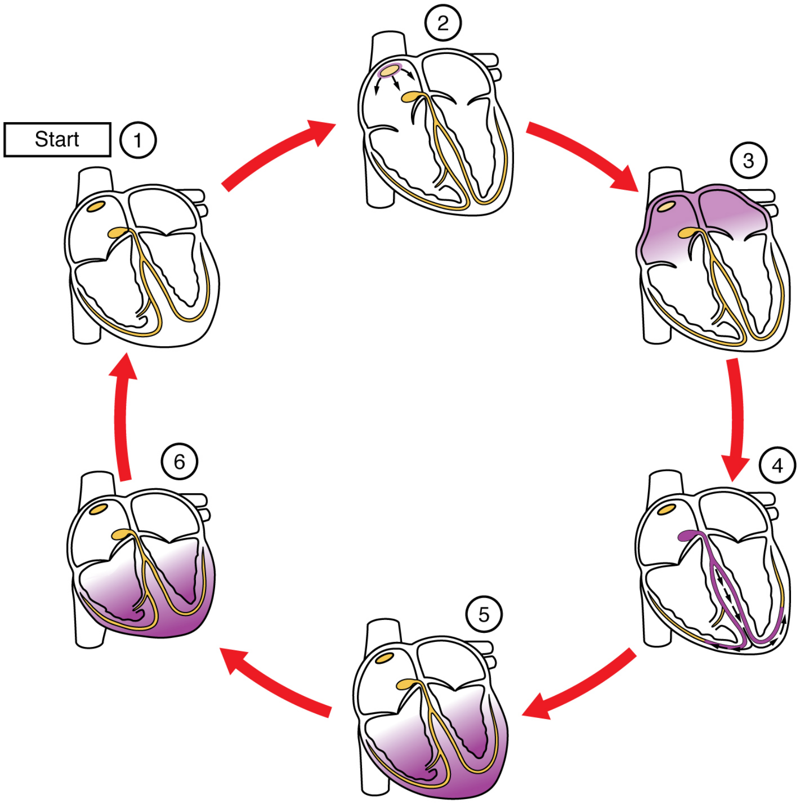
Sinoatrial (SA) Node

Normal cardiac rhythm is established by the **sinoatrial (SA) node**, a specialized clump of myocardial conducting cells located in the superior

and posterior walls of the right atrium in close proximity to the orifice of the superior vena cava. The SA node has the highest inherent rate of depolarization and is known as the **pacemaker** of the heart. It initiates the **sinus rhythm**, or normal electrical pattern followed by contraction of the heart.

This impulse spreads from its initiation in the SA node throughout the atria through specialized **internodal pathways**, to the atrial myocardial contractile cells and the atrioventricular node. The internodal pathways consist of three bands (anterior, middle, and posterior) that lead directly from the SA node to the next node in the conduction system, the atrioventricular node (see [link]). The impulse takes approximately 50 ms (milliseconds) to travel between these two nodes. The relative importance of this pathway has been debated since the impulse would reach the atrioventricular node simply following the cell-by-cell pathway through the contractile cells of the myocardium in the atria. In addition, there is a specialized pathway called **Bachmann's bundle** or the **interatrial band** that conducts the impulse directly from the right atrium to the left atrium. Regardless of the pathway, as the impulse reaches the atrioventricular septum, the connective tissue of the cardiac skeleton prevents the impulse from spreading into the myocardial cells in the ventricles except at the atrioventricular node. [link] illustrates the initiation of the impulse in the SA node that then spreads the impulse throughout the atria to the atrioventricular node.

Cardiac Conduction



(1) The sinoatrial (SA) node and the remainder of the conduction system are at rest. (2) The SA node initiates the action potential, which sweeps across the atria. (3) After reaching the atrioventricular node, there is a delay of approximately 100 ms that allows the atria to complete pumping blood before the impulse is transmitted to the atrioventricular bundle. (4) Following the delay, the impulse travels through the atrioventricular bundle and bundle branches to the Purkinje fibers, and also reaches the right papillary muscle via the moderator band. (5) The impulse spreads to the contractile fibers of the ventricle. (6) Ventricular contraction begins.

The electrical event, the wave of depolarization, is the trigger for muscular contraction. The wave of depolarization begins in the right atrium, and the impulse spreads across the superior portions of both atria and then down through the contractile cells. The contractile cells then begin contraction from the superior to the inferior portions of the atria, efficiently pumping blood into the ventricles.

Atrioventricular (AV) Node

The **atrioventricular (AV) node** is a second clump of specialized myocardial conductive cells, located in the inferior portion of the right atrium within the atrioventricular septum. The septum prevents the impulse from spreading directly to the ventricles without passing through the AV node. There is a critical pause before the AV node depolarizes and transmits the impulse to the atrioventricular bundle (see [link], step 3). This delay in transmission is partially attributable to the small diameter of the cells of the node, which slow the impulse. Also, conduction between nodal cells is less efficient than between conducting cells. These factors mean that it takes the impulse approximately 100 ms to pass through the node. This pause is critical to heart function, as it allows the atrial cardiomyocytes to complete their contraction that pumps blood into the ventricles before the impulse is transmitted to the cells of the ventricle itself. With extreme stimulation by the SA node, the AV node can transmit impulses maximally at 220 per minute. This establishes the typical maximum heart rate in a healthy young individual. Damaged hearts or those stimulated by drugs can contract at higher rates, but at these rates, the heart can no longer effectively pump blood.

Atrioventricular Bundle (Bundle of His), Bundle Branches, and Purkinje Fibers

Arising from the AV node, the **atrioventricular bundle**, or **bundle of His**, proceeds through the interventricular septum before dividing into two **atrioventricular bundle branches**, commonly called the left and right

bundle branches. The left bundle branch has two fascicles. The left bundle branch supplies the left ventricle, and the right bundle branch the right ventricle. Since the left ventricle is much larger than the right, the left bundle branch is also considerably larger than the right. Portions of the right bundle branch are found in the moderator band and supply the right papillary muscles. Because of this connection, each papillary muscle receives the impulse at approximately the same time, so they begin to contract simultaneously just prior to the remainder of the myocardial contractile cells of the ventricles. This is believed to allow tension to develop on the chordae tendineae prior to right ventricular contraction. There is no corresponding moderator band on the left. Both bundle branches descend and reach the apex of the heart where they connect with the Purkinje fibers (see [link], step 4). This passage takes approximately 25 ms.

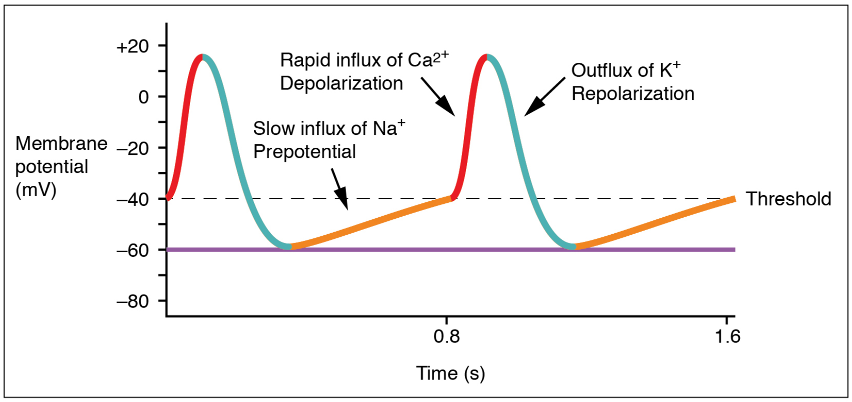
The **Purkinje fibers** are additional myocardial conductive fibers that spread the impulse to the myocardial contractile cells in the ventricles. They extend throughout the myocardium from the apex of the heart toward the atrioventricular septum and the base of the heart. The Purkinje fibers have a fast inherent conduction rate, and the electrical impulse reaches all of the ventricular muscle cells in about 75 ms (see [link], step 5). Since the electrical stimulus begins at the apex, the contraction also begins at the apex and travels toward the base of the heart, similar to squeezing a tube of toothpaste from the bottom. This allows the blood to be pumped out of the ventricles and into the aorta and pulmonary trunk. The total time elapsed from the initiation of the impulse in the SA node until depolarization of the ventricles is approximately 225 ms.

Membrane Potentials and Ion Movement in Cardiac Conductive Cells

Action potentials are considerably different between cardiac conductive cells and cardiac contractive cells. While Na^+ and K^+ play essential roles, Ca^{2+} is also critical for both types of cells. Unlike skeletal muscles and neurons, cardiac conductive cells do not have a stable resting potential. Conductive cells contain a series of sodium ion channels that allow a normal and slow influx of sodium ions that causes the membrane potential

to rise slowly from an initial value of −60 mV up to about –40 mV. The resulting movement of sodium ions creates **spontaneous depolarization** (or **prepotential depolarization**). At this point, calcium ion channels open and Ca^{2+} enters the cell, further depolarizing it at a more rapid rate until it reaches a value of approximately +5 mV. At this point, the calcium ion channels close and K^{+} channels open, allowing outflux of K^{+} and resulting in repolarization. When the membrane potential reaches approximately −60 mV, the K^{+} channels close and Na^{+} channels open, and the prepotential phase begins again. This phenomenon explains the autorhythmicity properties of cardiac muscle ([link]).

Action Potential at the SA Node



The prepotential is due to a slow influx of sodium ions until the threshold is reached followed by a rapid depolarization and repolarization. The prepotential accounts for the membrane reaching threshold and initiates the spontaneous depolarization and contraction of the cell. Note the lack of a resting potential.

Membrane Potentials and Ion Movement in Cardiac Contractile Cells

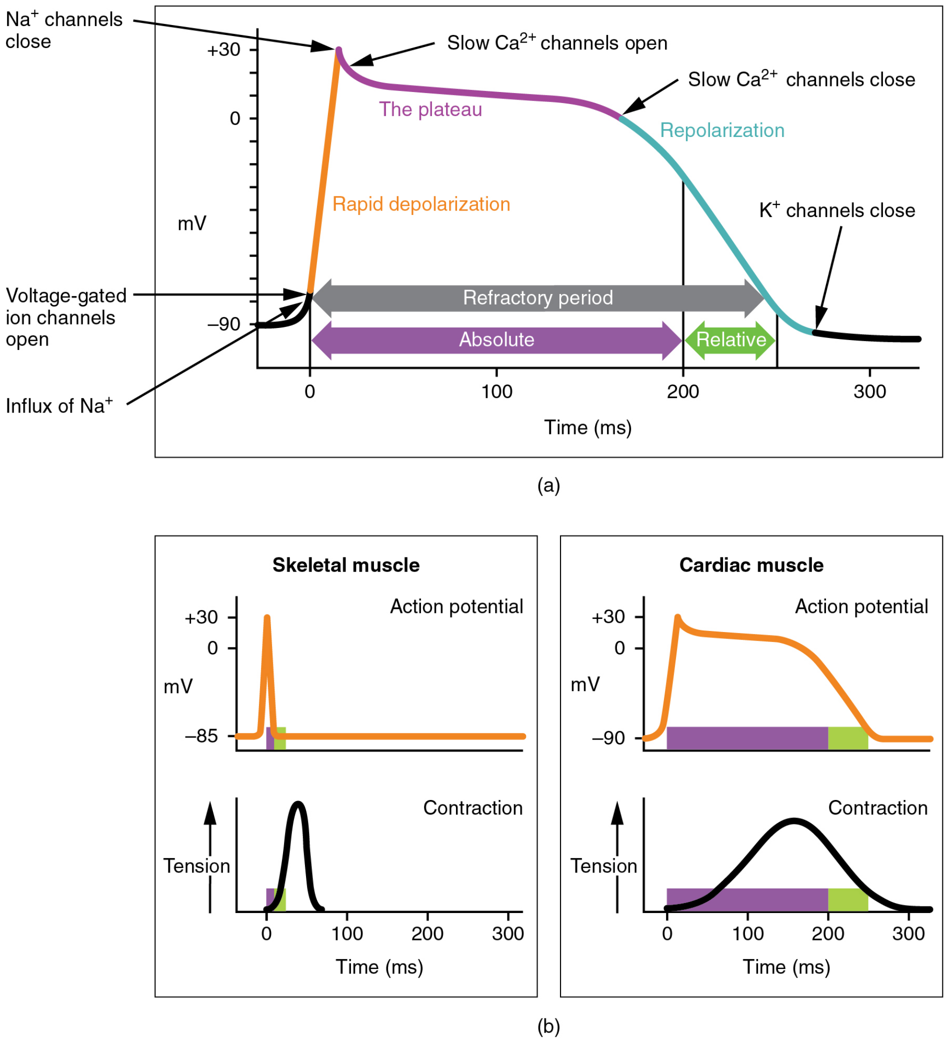
There is a distinctly different electrical pattern involving the contractile cells. In this case, there is a rapid depolarization, followed by a plateau

phase and then repolarization. This phenomenon accounts for the long refractory periods required for the cardiac muscle cells to pump blood effectively before they are capable of firing for a second time. These cardiac myocytes normally do not initiate their own electrical potential but rather wait for an impulse to reach them.

Contractile cells demonstrate a much more stable resting phase than conductive cells at approximately −80 mV for cells in the atria and −90 mV for cells in the ventricles. Despite this initial difference, the other components of their action potentials are virtually identical. In both cases, when stimulated by an action potential, voltage-gated channels rapidly open, beginning the positive-feedback mechanism of depolarization. This rapid influx of positively charged ions raises the membrane potential to approximately +30 mV, at which point the sodium channels close. The rapid depolarization period typically lasts 3–5 ms. Depolarization is followed by the plateau phase, in which membrane potential declines relatively slowly. This is due in large part to the opening of the slow Ca^{2+} channels, allowing Ca^{2+} to enter the cell while few K^+ channels are open, allowing K^+ to exit the cell. The relatively long plateau phase lasts approximately 175 ms. Once the membrane potential reaches approximately zero, the Ca^{2+} channels close and K^+ channels open, allowing K^+ to exit the cell. The repolarization lasts approximately 75 ms. At this point, membrane potential drops until it reaches resting levels once more and the cycle repeats. The entire event lasts between 250 and 300 ms ([link]).

The absolute refractory period for cardiac contractile muscle lasts approximately 200 ms, and the relative refractory period lasts approximately 50 ms, for a total of 250 ms. This extended period is critical, since the heart muscle must contract to pump blood effectively and the contraction must follow the electrical events. Without extended refractory periods, premature contractions would occur in the heart and would not be compatible with life.

Action Potential in Cardiac Contractile Cells



(a) Note the long plateau phase due to the influx of calcium ions. The extended refractory period allows the cell to fully contract before another electrical event can occur. (b) The action potential for heart muscle is compared to that of skeletal muscle.

Calcium Ions

Calcium ions play two critical roles in the physiology of cardiac muscle. Their influx through slow calcium channels accounts for the prolonged plateau phase and absolute refractory period that enable cardiac muscle to function properly. Calcium ions also combine with the regulatory protein troponin in the troponin-tropomyosin complex; this complex removes the inhibition that prevents the heads of the myosin molecules from forming cross bridges with the active sites on actin that provide the power stroke of contraction. This mechanism is virtually identical to that of skeletal muscle. Approximately 20 percent of the calcium required for contraction is supplied by the influx of Ca^{2+} during the plateau phase. The remaining Ca^{2+} for contraction is released from storage in the sarcoplasmic reticulum.

Comparative Rates of Conduction System Firing

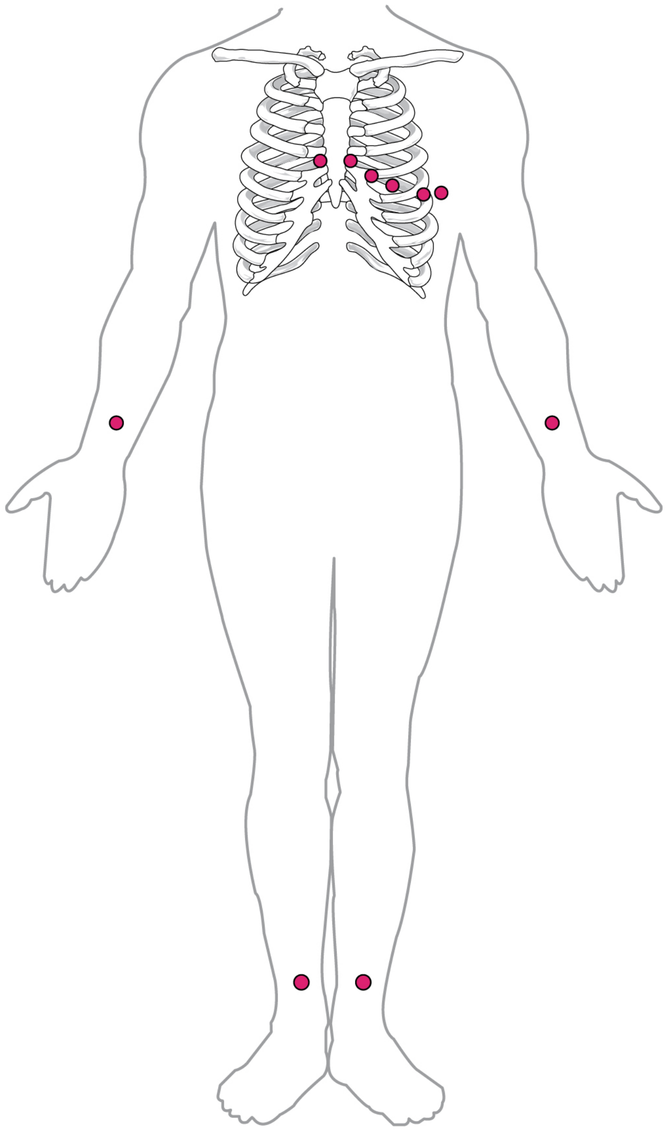
The pattern of prepotential or spontaneous depolarization, followed by rapid depolarization and repolarization just described, are seen in the SA node and a few other conductive cells in the heart. Since the SA node is the pacemaker, it reaches threshold faster than any other component of the conduction system. It will initiate the impulses spreading to the other conducting cells. The SA node, without nervous or endocrine control, would initiate a heart impulse approximately 80–100 times per minute. Although each component of the conduction system is capable of generating its own impulse, the rate progressively slows as you proceed from the SA node to the Purkinje fibers. Without the SA node, the AV node would generate a heart rate of 40–60 beats per minute. If the AV node were blocked, the atrioventricular bundle would fire at a rate of approximately 30–40 impulses per minute. The bundle branches would have an inherent rate of 20–30 impulses per minute, and the Purkinje fibers would fire at 15–20 impulses per minute. While a few exceptionally trained aerobic athletes demonstrate resting heart rates in the range of 30–40 beats per minute (the lowest recorded figure is 28 beats per minute for Miguel Indurain, a cyclist), for most individuals, rates lower than 50 beats per minute would indicate a condition called bradycardia. Depending upon the specific individual, as rates fall much below this level, the heart would be unable to maintain adequate flow of blood to vital tissues, initially resulting in

decreasing loss of function across the systems, unconsciousness, and ultimately death.

Electrocardiogram

By careful placement of surface electrodes on the body, it is possible to record the complex, compound electrical signal of the heart. This tracing of the electrical signal is the **electrocardiogram (ECG)**, also commonly abbreviated EKG (K coming kardiology, from the German term for cardiology). Careful analysis of the ECG reveals a detailed picture of both normal and abnormal heart function, and is an indispensable clinical diagnostic tool. The standard electrocardiograph (the instrument that generates an ECG) uses 3, 5, or 12 leads. The greater the number of leads an electrocardiograph uses, the more information the ECG provides. The term “lead” may be used to refer to the cable from the electrode to the electrical recorder, but it typically describes the voltage difference between two of the electrodes. The 12-lead electrocardiograph uses 10 electrodes placed in standard locations on the patient’s skin ([link]). In continuous ambulatory electrocardiographs, the patient wears a small, portable, battery-operated device known as a Holter monitor, or simply a Holter, that continuously monitors heart electrical activity, typically for a period of 24 hours during the patient’s normal routine.

Standard Placement of ECG Leads



In a 12-lead ECG, six electrodes are placed on the chest, and four electrodes are placed on the limbs.

A normal ECG tracing is presented in [link]. Each component, segment, and interval is labeled and corresponds to important electrical events, demonstrating the relationship between these events and contraction in the heart.

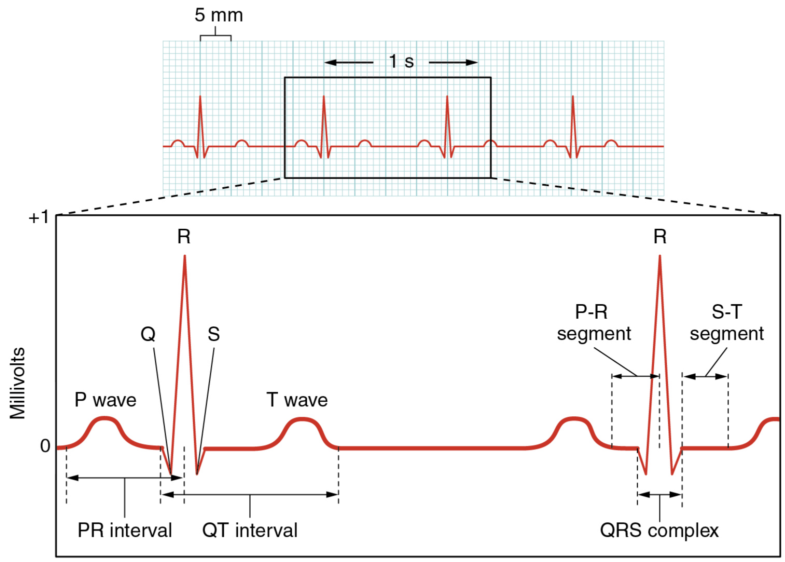
There are five prominent points on the ECG: the P wave, the QRS complex, and the T wave. The small **P wave** represents the depolarization of the atria. The atria begin contracting approximately 25 ms after the start of the P wave. The large **QRS complex** represents the depolarization of the ventricles, which requires a much stronger electrical signal because of the larger size of the ventricular cardiac muscle. The ventricles begin to contract as the QRS reaches the peak of the R wave. Lastly, the **T wave** represents the repolarization of the ventricles. The repolarization of the atria occurs during the QRS complex, which masks it on an ECG.

The major segments and intervals of an ECG tracing are indicated in [link]. Segments are defined as the regions between two waves. Intervals include one segment plus one or more waves. For example, the PR segment begins at the end of the P wave and ends at the beginning of the QRS complex. The PR interval starts at the beginning of the P wave and ends with the beginning of the QRS complex. The PR interval is more clinically relevant, as it measures the duration from the beginning of atrial depolarization (the P wave) to the initiation of the QRS complex. Since the Q wave may be difficult to view in some tracings, the measurement is often extended to the R that is more easily visible. Should there be a delay in passage of the impulse from the SA node to the AV node, it would be visible in the PR interval. [link] correlates events of heart contraction to the corresponding segments and intervals of an ECG.

Note:

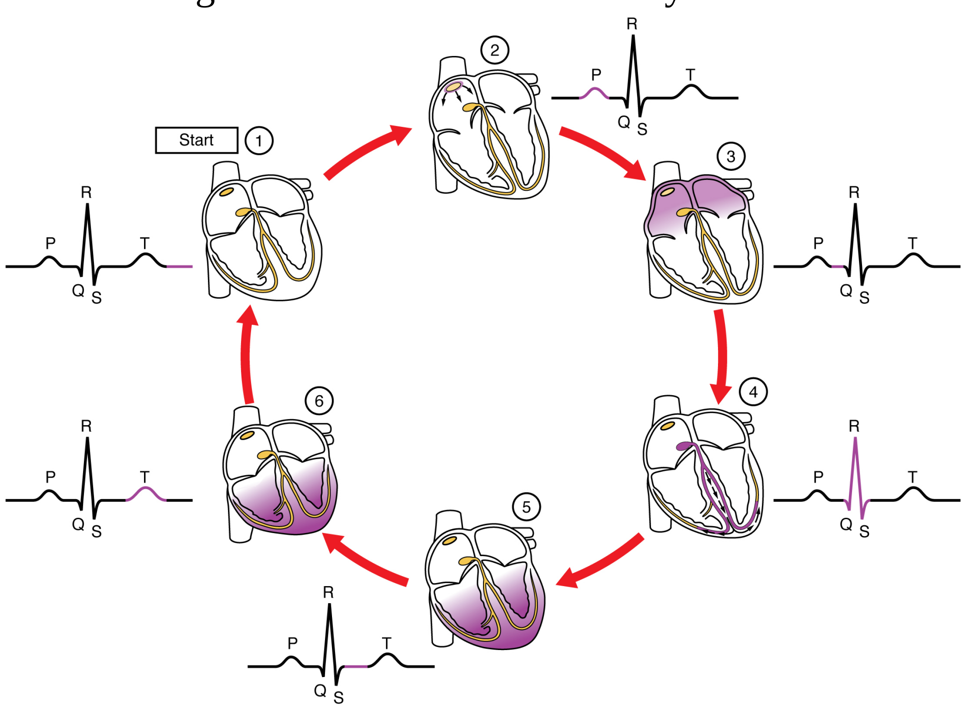
Visit this site for a more detailed analysis of ECGs.

Electrocardiogram



A normal tracing shows the P wave, QRS complex, and T wave. Also indicated are the PR, QT, QRS, and ST intervals, plus the P-R and S-T segments.

ECG Tracing Correlated to the Cardiac Cycle



This diagram correlates an ECG tracing with the electrical and mechanical events of a heart contraction. Each segment of an ECG tracing corresponds to one event in the cardiac cycle.

Note:

Everyday Connection

ECG Abnormalities

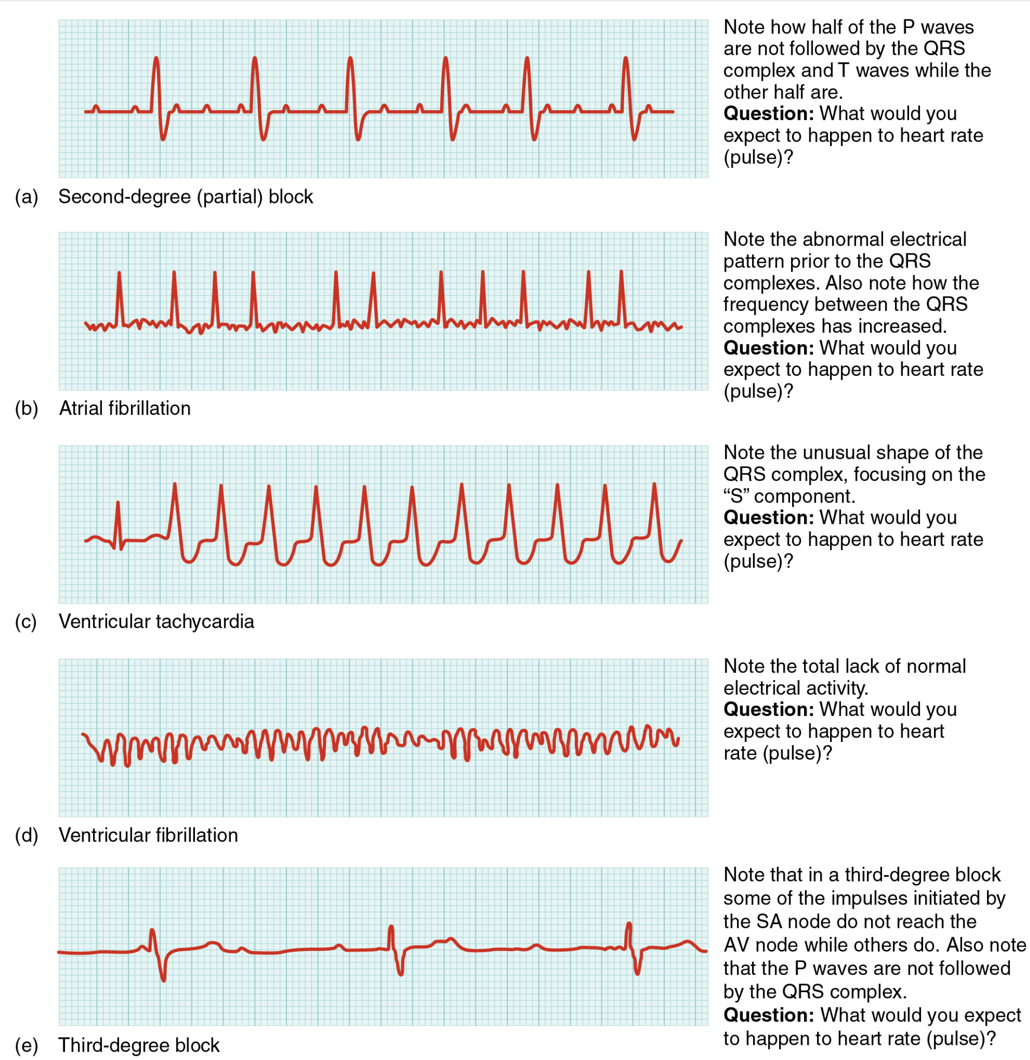
Occassionally, an area of the heart other than the SA node will initiate an impulse that will be followed by a premature contraction. Such an area, which may actually be a component of the conduction system or some other contractile cells, is known as an ectopic focus or ectopic pacemaker. An ectopic focus may be stimulated by localized ischemia; exposure to certain drugs, including caffeine, digitalis, or acetylcholine; elevated stimulation by both sympathetic or parasympathetic divisions of the autonomic nervous system; or a number of disease or pathological conditions. Occasional occurances are generally transitory and nonlife threatening, but if the condition becomes chronic, it may lead to either an arrhythmia, a deviation from the normal pattern of impulse conduction and contraction, or to fibrillation, an uncoordinated beating of the heart.

While interpretation of an ECG is possible and extremely valuable after some training, a full understanding of the complexities and intricacies generally requires several years of experience. In general, the size of the electrical variations, the duration of the events, and detailed vector analysis provide the most comprehensive picture of cardiac function. For example, an amplified P wave may indicate enlargement of the atria, an enlarged Q wave may indicate a MI, and an enlarged suppressed or inverted Q wave often indicates enlarged ventricles. T waves often appear flatter when insufficient oxygen is being delivered to the myocardium. An elevation of the ST segment above baseline is often seen in patients with an acute MI, and may appear depressed below the baseline when hypoxia is occurring.

As useful as analyzing these electrical recordings may be, there are limitations. For example, not all areas suffering a MI may be obvious on

the ECG. Additionally, it will not reveal the effectiveness of the pumping, which requires further testing, such as an ultrasound test called an echocardiogram or nuclear medicine imaging. It is also possible for there to be pulseless electrical activity, which will show up on an ECG tracing, although there is no corresponding pumping action. Common abnormalities that may be detected by the ECGs are shown in [link].

Common ECG Abnormalities



(a) In a second-degree or partial block, one-half of the P waves are not followed by the QRS complex and T waves while the other half are. (b) In atrial fibrillation, the electrical pattern is abnormal prior to the QRS complex, and the frequency between the QRS complexes has increased. (c) In ventricular tachycardia, the shape of the

QRS complex is abnormal. (d) In ventricular fibrillation, there is no normal electrical activity. (e) In a third-degree block, there is no correlation between atrial activity (the P wave) and ventricular activity (the QRS complex).

Note:

Visit this site for a more complete library of abnormal ECGs.

Note:

Everyday Connection

External Automated Defibrillators

In the event that the electrical activity of the heart is severely disrupted, cessation of electrical activity or fibrillation may occur. In fibrillation, the heart beats in a wild, uncontrolled manner, which prevents it from being able to pump effectively. Atrial fibrillation (see [link]**b**) is a serious condition, but as long as the ventricles continue to pump blood, the patient’s life may not be in immediate danger. Ventricular fibrillation (see [link]**d**) is a medical emergency that requires life support, because the ventricles are not effectively pumping blood. In a hospital setting, it is often described as “code blue.” If untreated for as little as a few minutes, ventricular fibrillation may lead to brain death. The most common treatment is defibrillation, which uses special paddles to apply a charge to the heart from an external electrical source in an attempt to establish a normal sinus rhythm ([link]). A defibrillator effectively stops the heart so

that the SA node can trigger a normal conduction cycle. Because of their effectiveness in reestablishing a normal sinus rhythm, external automated defibrillators (EADs) are being placed in areas frequented by large numbers of people, such as schools, restaurants, and airports. These devices contain simple and direct verbal instructions that can be followed by nonmedical personnel in an attempt to save a life.

Defibrillators

(a) An external automatic defibrillator can be used by nonmedical personnel to reestablish a normal sinus rhythm in a person with fibrillation. (b) Defibrillator paddles are more commonly used in hospital settings. (credit b: “widerider107”/flickr.com)

A **heart block** refers to an interruption in the normal conduction pathway. The nomenclature for these is very straightforward. SA nodal blocks occur within the SA node. AV nodal blocks occur within the AV node. Infra-Hisian blocks involve the bundle of His. Bundle branch blocks occur within either the left or right atrioventricular bundle branches. Hemiblocks are partial and occur within one or more fascicles of the atrioventricular bundle branch. Clinically, the most common types are the AV nodal and infra-Hisian blocks.

AV blocks are often described by degrees. A first-degree or partial block indicates a delay in conduction between the SA and AV nodes. This can be recognized on the ECG as an abnormally long PR interval. A second-degree or incomplete block occurs when some impulses from the SA node reach the AV node and continue, while others do not. In this instance, the ECG would reveal some P waves not followed by a QRS complex, while others would appear normal. In the third-degree or complete block, there is no correlation between atrial activity (the P wave) and ventricular activity (the QRS complex). Even in the event of a total SA block, the AV node will assume the role of pacemaker and continue initiating contractions at 40–60 contractions per minute, which is adequate to maintain consciousness. Second- and third-degree blocks are demonstrated on the ECG presented in [link].

When arrhythmias become a chronic problem, the heart maintains a junctional rhythm, which originates in the AV node. In order to speed up the heart rate and restore full sinus rhythm, a cardiologist can implant an **artificial pacemaker**, which delivers electrical impulses to the heart muscle to ensure that the heart continues to contract and pump blood effectively. These artificial pacemakers are programmable by the cardiologists and can either provide stimulation temporarily upon demand or on a continuous basis. Some devices also contain built-in defibrillators.

Cardiac Muscle Metabolism

Normally, cardiac muscle metabolism is entirely aerobic. Oxygen from the lungs is brought to the heart, and every other organ, attached to the hemoglobin molecules within the erythrocytes. Heart cells also store appreciable amounts of oxygen in myoglobin. Normally, these two mechanisms, circulating oxygen and oxygen attached to myoglobin, can supply sufficient oxygen to the heart, even during peak performance.

Fatty acids and glucose from the circulation are broken down within the mitochondria to release energy in the form of ATP. Both fatty acid droplets and glycogen are stored within the sarcoplasm and provide additional nutrient supply. (Seek additional content for more detail about metabolism.)

Chapter Review

The heart is regulated by both neural and endocrine control, yet it is capable of initiating its own action potential followed by muscular contraction. The conductive cells within the heart establish the heart rate and transmit it through the myocardium. The contractile cells contract and propel the blood. The normal path of transmission for the conductive cells is the sinoatrial (SA) node, internodal pathways, atrioventricular (AV) node, atrioventricular (AV) bundle of His, bundle branches, and Purkinje fibers. The action potential for the conductive cells consists of a prepotential phase with a slow influx of Na^+ followed by a rapid influx of Ca^{2+} and outflux of K^+. Contractile cells have an action potential with an extended plateau phase that results in an extended refractory period to allow complete contraction for the heart to pump blood effectively. Recognizable points on the ECG include the P wave that corresponds to atrial depolarization, the QRS complex that corresponds to ventricular depolarization, and the T wave that corresponds to ventricular repolarization.

Review Questions

Exercise:

Problem: Which of the following is unique to cardiac muscle cells?

a. Only cardiac muscle contains a sarcoplasmic reticulum.
b. Only cardiac muscle has gap junctions.
c. Only cardiac muscle is capable of autorhythmicity
d. Only cardiac muscle has a high concentration of mitochondria.

Solution:

C

Exercise:

Problem: The influx of which ion accounts for the plateau phase?

a. sodium
b. potassium
c. chloride
d. calcium

Solution:

D

Exercise:

Problem:

Which portion of the ECG corresponds to repolarization of the atria?

a. P wave
b. QRS complex
c. T wave
d. none of the above: atrial repolarization is masked by ventricular depolarization

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Solution:

D

Exercise:

Problem:

Which component of the heart conduction system would have the slowest rate of firing?

a. atrioventricular node
b. atrioventricular bundle
c. bundle branches
d. Purkinje fibers

Solution:

D

Critical Thinking Questions

Exercise:

Problem:

Why is the plateau phase so critical to cardiac muscle function?

Solution:

It prevents additional impulses from spreading through the heart prematurely, thereby allowing the muscle sufficient time to contract and pump blood effectively.

Exercise:

Problem:

How does the delay of the impulse at the atrioventricular node contribute to cardiac function?

Solution:

It ensures sufficient time for the atrial muscle to contract and pump blood into the ventricles prior to the impulse being conducted into the lower chambers.

Exercise:

Problem:

How do gap junctions and intercalated disks aid contraction of the heart?

Solution:

Gap junctions within the intercalated disks allow impulses to spread from one cardiac muscle cell to another, allowing sodium, potassium,

and calcium ions to flow between adjacent cells, propagating the action potential, and ensuring coordinated contractions.

Exercise:

Problem:

Why do the cardiac muscles cells demonstrate autorhythmicity?

Solution:

Without a true resting potential, there is a slow influx of sodium ions through slow channels that produces a prepotential that gradually reaches threshold.

Glossary

artificial pacemaker
: medical device that transmits electrical signals to the heart to ensure that it contracts and pumps blood to the body

atrioventricular bundle
: (also, bundle of His) group of specialized myocardial conductile cells that transmit the impulse from the AV node through the interventricular septum; form the left and right atrioventricular bundle branches

atrioventricular bundle branches
: (also, left or right bundle branches) specialized myocardial conductile cells that arise from the bifurcation of the atrioventricular bundle and pass through the interventricular septum; lead to the Purkinje fibers and also to the right papillary muscle via the moderator band

atrioventricular (AV) node
: clump of myocardial cells located in the inferior portion of the right atrium within the atrioventricular septum; receives the impulse from the SA node, pauses, and then transmits it into specialized conducting cells within the interventricular septum

autorhythmicity

ability of cardiac muscle to initiate its own electrical impulse that triggers the mechanical contraction that pumps blood at a fixed pace without nervous or endocrine control

Bachmann’s bundle

(also, interatrial band) group of specialized conducting cells that transmit the impulse directly from the SA node in the right atrium to the left atrium

bundle of His

(also, atrioventricular bundle) group of specialized myocardial conductile cells that transmit the impulse from the AV node through the interventricular septum; form the left and right atrioventricular bundle branches

electrocardiogram (ECG)

surface recording of the electrical activity of the heart that can be used for diagnosis of irregular heart function; also abbreviated as EKG

heart block

interruption in the normal conduction pathway

interatrial band

(also, Bachmann’s bundle) group of specialized conducting cells that transmit the impulse directly from the SA node in the right atrium to the left atrium

intercalated disc

physical junction between adjacent cardiac muscle cells; consisting of desmosomes, specialized linking proteoglycans, and gap junctions that allow passage of ions between the two cells

internodal pathways

specialized conductile cells within the atria that transmit the impulse from the SA node throughout the myocardial cells of the atrium and to the AV node

myocardial conducting cells
: specialized cells that transmit electrical impulses throughout the heart and trigger contraction by the myocardial contractile cells

myocardial contractile cells
: bulk of the cardiac muscle cells in the atria and ventricles that conduct impulses and contract to propel blood

P wave
: component of the electrocardiogram that represents the depolarization of the atria

pacemaker
: cluster of specialized myocardial cells known as the SA node that initiates the sinus rhythm

prepotential depolarization
: (also, spontaneous depolarization) mechanism that accounts for the autorhythmic property of cardiac muscle; the membrane potential increases as sodium ions diffuse through the always-open sodium ion channels and causes the electrical potential to rise

Purkinje fibers
: specialized myocardial conduction fibers that arise from the bundle branches and spread the impulse to the myocardial contraction fibers of the ventricles

QRS complex
: component of the electrocardiogram that represents the depolarization of the ventricles and includes, as a component, the repolarization of the atria

sinoatrial (SA) node
: known as the pacemaker, a specialized clump of myocardial conducting cells located in the superior portion of the right atrium that has the highest inherent rate of depolarization that then spreads throughout the heart

sinus rhythm
: normal contractile pattern of the heart

spontaneous depolarization
: (also, prepotential depolarization) the mechanism that accounts for the autorhythmic property of cardiac muscle; the membrane potential increases as sodium ions diffuse through the always-open sodium ion channels and causes the electrical potential to rise

T wave
: component of the electrocardiogram that represents the repolarization of the ventricles

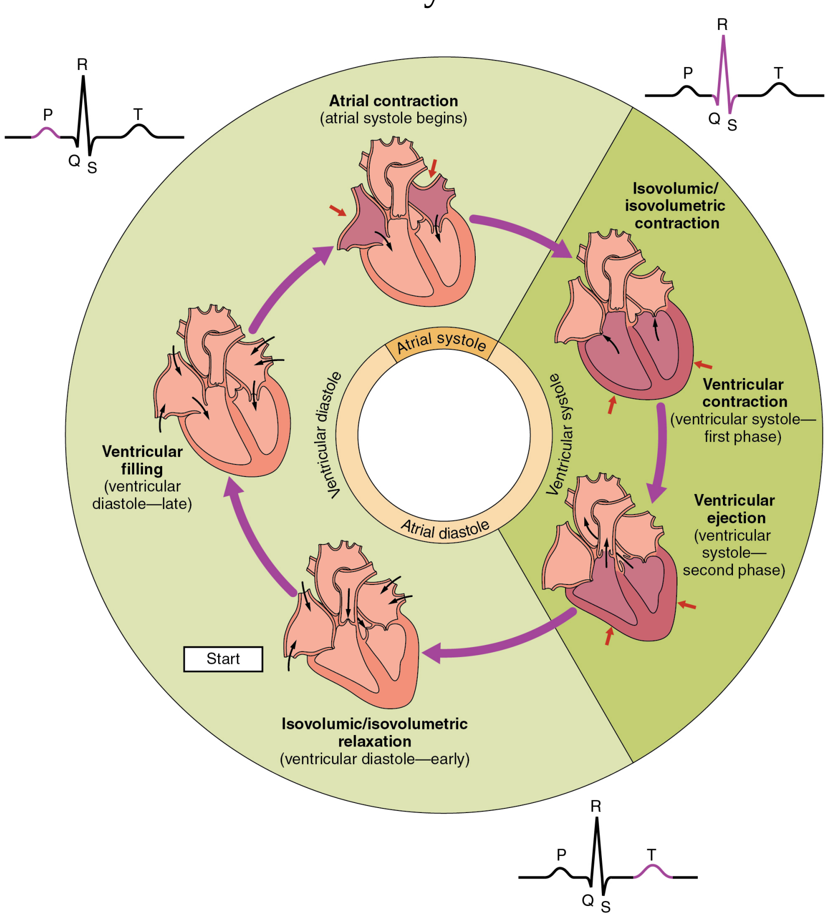
Cardiac Cycle

By the end of this section, you will be able to:

- Describe the relationship between blood pressure and blood flow
- Summarize the events of the cardiac cycle
- Compare atrial and ventricular systole and diastole
- Relate heart sounds detected by auscultation to action of heart’s valves

The period of time that begins with contraction of the atria and ends with ventricular relaxation is known as the **cardiac cycle** ([link]). The period of contraction that the heart undergoes while it pumps blood into circulation is called **systole**. The period of relaxation that occurs as the chambers fill with blood is called **diastole**. Both the atria and ventricles undergo systole and diastole, and it is essential that these components be carefully regulated and coordinated to ensure blood is pumped efficiently to the body.

Overview of the Cardiac Cycle



The cardiac cycle begins with atrial systole and progresses to ventricular systole, atrial diastole, and ventricular diastole, when the cycle begins again. Correlations to the ECG are highlighted.

Pressures and Flow

Fluids, whether gases or liquids, are materials that flow according to pressure gradients—that is, they move from regions that are higher in pressure to regions that are lower in pressure. Accordingly, when the heart chambers are relaxed (diastole), blood will flow into the atria from the veins, which are higher in pressure. As blood flows into the atria, the pressure will rise, so the blood will initially move passively from the atria into the ventricles. When the action potential triggers the muscles in the atria to contract (atrial systole), the pressure within the atria rises further, pumping blood into the ventricles. During ventricular systole, pressure rises in the ventricles, pumping blood into the pulmonary trunk from the right ventricle and into the aorta from the left ventricle. Again, as you consider this flow and relate it to the conduction pathway, the elegance of the system should become apparent.

Phases of the Cardiac Cycle

At the beginning of the cardiac cycle, both the atria and ventricles are relaxed (diastole). Blood is flowing into the right atrium from the superior and inferior venae cavae and the coronary sinus. Blood flows into the left atrium from the four pulmonary veins. The two atrioventricular valves, the tricuspid and mitral valves, are both open, so blood flows unimpeded from the atria and into the ventricles. Approximately 70–80 percent of ventricular filling occurs by this method. The two semilunar valves, the pulmonary and aortic valves, are closed, preventing backflow of blood into the right and left ventricles from the pulmonary trunk on the right and the aorta on the left.

Atrial Systole and Diastole

Contraction of the atria follows depolarization, represented by the P wave of the ECG. As the atrial muscles contract from the superior portion of the atria toward the atrioventricular septum, pressure rises within the atria and blood is pumped into the ventricles through the open atrioventricular (tricuspid, and mitral or bicuspid) valves. At the start of atrial systole, the ventricles are normally filled with approximately 70–80 percent of their capacity due to inflow during diastole. Atrial contraction, also referred to as the “atrial kick,” contributes the remaining 20–30 percent of filling (see [link]). Atrial systole lasts approximately 100 ms and ends prior to ventricular systole, as the atrial muscle returns to diastole.

Ventricular Systole

Ventricular systole (see [link]) follows the depolarization of the ventricles and is represented by the QRS complex in the ECG. It may be conveniently divided into two phases, lasting a total of 270 ms. At the end of atrial systole and just prior to atrial contraction, the ventricles contain approximately 130 mL blood in a resting adult in a standing position. This volume is known as the **end diastolic volume (EDV)** or **preload**.

Initially, as the muscles in the ventricle contract, the pressure of the blood within the chamber rises, but it is not yet high enough to open the semilunar (pulmonary and aortic) valves and be ejected from the heart. However, blood pressure quickly rises above that of the atria that are now relaxed and in diastole. This increase in pressure causes blood to flow back toward the atria, closing the tricuspid and mitral valves. Since blood is not being ejected from the ventricles at this early stage, the volume of blood within the chamber remains constant. Consequently, this initial phase of ventricular systole is known as **isovolumic contraction**, also called isovolumetric contraction (see [link]).

In the second phase of ventricular systole, the **ventricular ejection phase**, the contraction of the ventricular muscle has raised the pressure within the ventricle to the point that it is greater than the pressures in the pulmonary

trunk and the aorta. Blood is pumped from the heart, pushing open the pulmonary and aortic semilunar valves. Pressure generated by the left ventricle will be appreciably greater than the pressure generated by the right ventricle, since the existing pressure in the aorta will be so much higher. Nevertheless, both ventricles pump the same amount of blood. This quantity is referred to as stroke volume. Stroke volume will normally be in the range of 70–80 mL. Since ventricular systole began with an EDV of approximately 130 mL of blood, this means that there is still 50–60 mL of blood remaining in the ventricle following contraction. This volume of blood is known as the **end systolic volume (ESV)**.

Ventricular Diastole

Ventricular relaxation, or diastole, follows repolarization of the ventricles and is represented by the T wave of the ECG. It too is divided into two distinct phases and lasts approximately 430 ms.

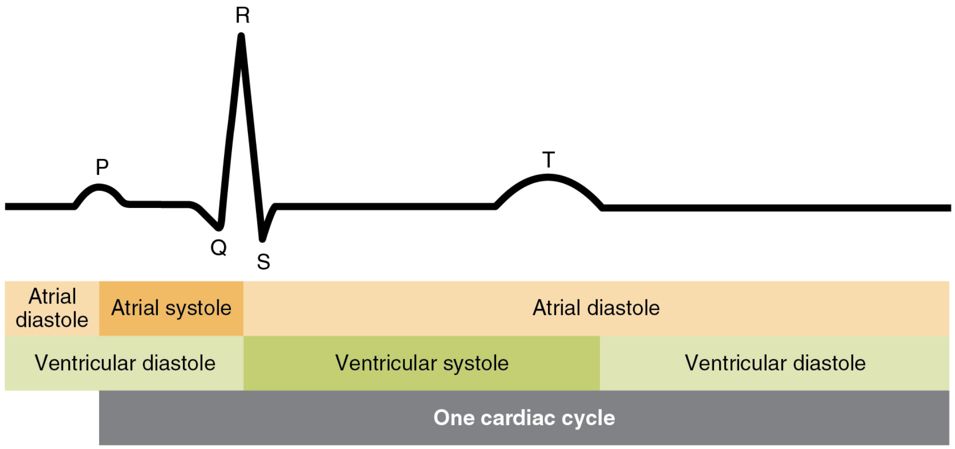
During the early phase of ventricular diastole, as the ventricular muscle relaxes, pressure on the remaining blood within the ventricle begins to fall. When pressure within the ventricles drops below pressure in both the pulmonary trunk and aorta, blood flows back toward the heart, producing the dicrotic notch (small dip) seen in blood pressure tracings. The semilunar valves close to prevent backflow into the heart. Since the atrioventricular valves remain closed at this point, there is no change in the volume of blood in the ventricle, so the early phase of ventricular diastole is called the **isovolumic ventricular relaxation phase**, also called isovolumetric ventricular relaxation phase (see [link]).

In the second phase of ventricular diastole, called late ventricular diastole, as the ventricular muscle relaxes, pressure on the blood within the ventricles drops even further. Eventually, it drops below the pressure in the atria. When this occurs, blood flows from the atria into the ventricles, pushing open the tricuspid and mitral valves. As pressure drops within the ventricles, blood flows from the major veins into the relaxed atria and from there into the ventricles. Both chambers are in diastole, the atrioventricular

valves are open, and the semilunar valves remain closed (see [link]). The cardiac cycle is complete.

[link] illustrates the relationship between the cardiac cycle and the ECG.

Relationship between the Cardiac Cycle and ECG



Initially, both the atria and ventricles are relaxed (diastole). The P wave represents depolarization of the atria and is followed by atrial contraction (systole). Atrial systole extends until the QRS complex, at which point, the atria relax. The QRS complex represents depolarization of the ventricles and is followed by ventricular contraction. The T wave represents the repolarization of the ventricles and marks the beginning of ventricular relaxation.

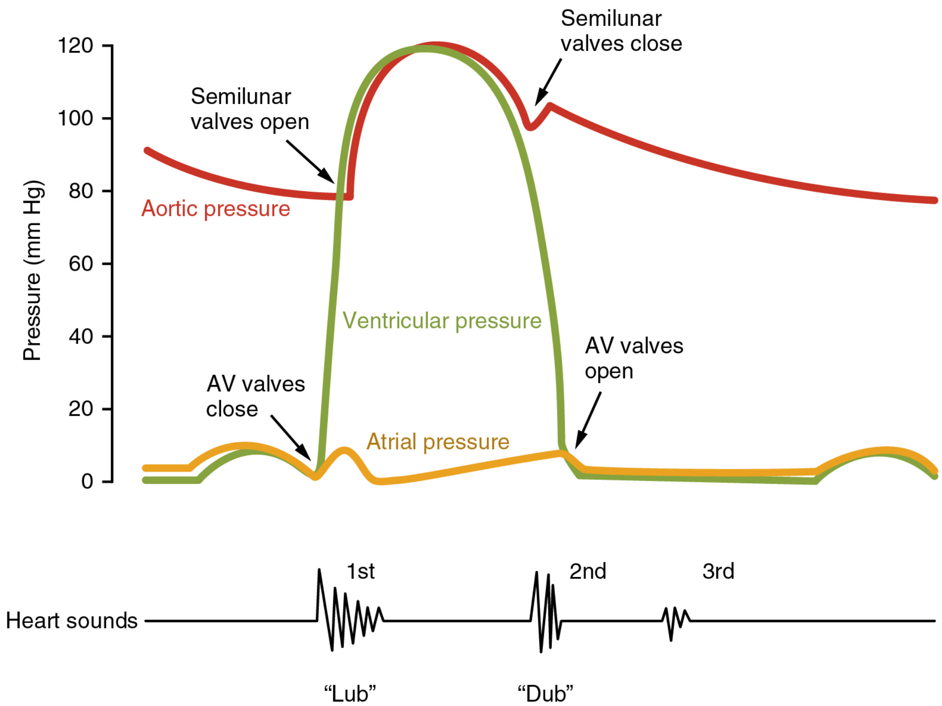
Heart Sounds

One of the simplest, yet effective, diagnostic techniques applied to assess the state of a patient's heart is auscultation using a stethoscope.

In a normal, healthy heart, there are only two audible **heart sounds**: S_1 and S_2. S_1 is the sound created by the closing of the atrioventricular valves during ventricular contraction and is normally described as a "lub," or first heart sound. The second heart sound, S_2, is the sound of the closing of the

semilunar valves during ventricular diastole and is described as a “dub” ([link]). In both cases, as the valves close, the openings within the atrioventricular septum guarded by the valves will become reduced, and blood flow through the opening will become more turbulent until the valves are fully closed. There is a third heart sound, S_3, but it is rarely heard in healthy individuals. It may be the sound of blood flowing into the atria, or blood sloshing back and forth in the ventricle, or even tensing of the chordae tendineae. S_3 may be heard in youth, some athletes, and pregnant women. If the sound is heard later in life, it may indicate congestive heart failure, warranting further tests. Some cardiologists refer to the collective S_1, S_2, and S_3 sounds as the “Kentucky gallop,” because they mimic those produced by a galloping horse. The fourth heart sound, S_4, results from the contraction of the atria pushing blood into a stiff or hypertrophic ventricle, indicating failure of the left ventricle. S_4 occurs prior to S_1 and the collective sounds S_4, S_1, and S_2 are referred to by some cardiologists as the “Tennessee gallop,” because of their similarity to the sound produced by a galloping horse with a different gait. A few individuals may have both S_3 and S_4, and this combined sound is referred to as S_7.

Heart Sounds and the Cardiac Cycle



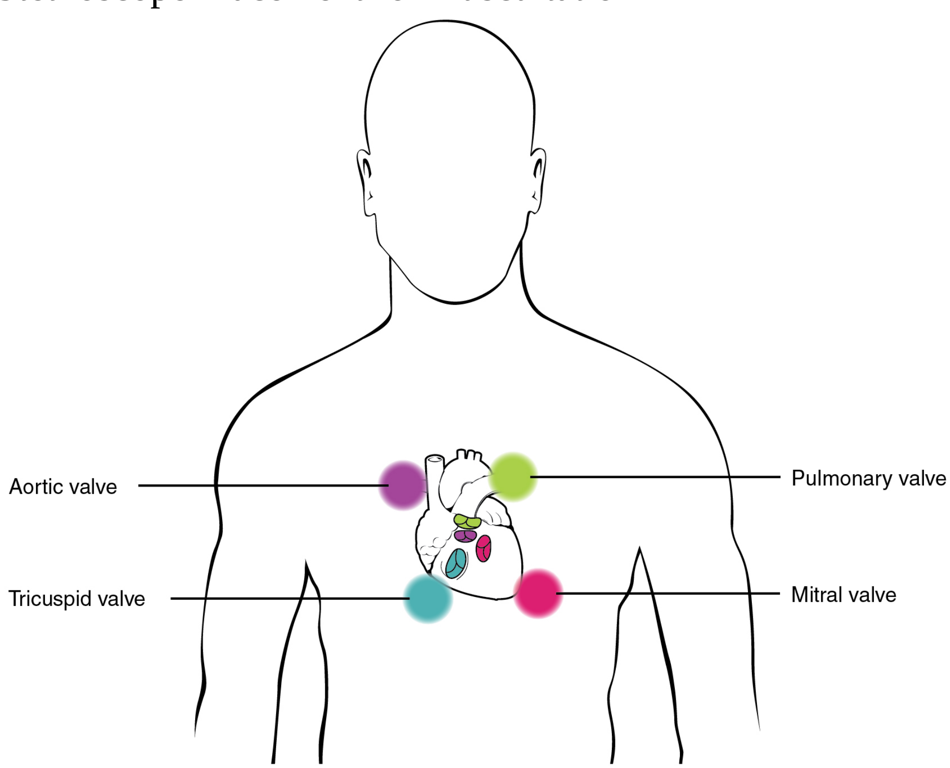
In this illustration, the x-axis reflects time with a

recording of the heart sounds. The y-axis represents pressure.

The term **murmur** is used to describe an unusual sound coming from the heart that is caused by the turbulent flow of blood. Murmurs are graded on a scale of 1 to 6, with 1 being the most common, the most difficult sound to detect, and the least serious. The most severe is a 6. Phonocardiograms or auscultograms can be used to record both normal and abnormal sounds using specialized electronic stethoscopes.

During auscultation, it is common practice for the clinician to ask the patient to breathe deeply. This procedure not only allows for listening to airflow, but it may also amplify heart murmurs. Inhalation increases blood flow into the right side of the heart and may increase the amplitude of right-sided heart murmurs. Expiration partially restricts blood flow into the left side of the heart and may amplify left-sided heart murmurs. [link] indicates proper placement of the bell of the stethoscope to facilitate auscultation.

Stethoscope Placement for Auscultation



Proper placement of the bell of the stethoscope facilitates auscultation. At each of the four locations on the chest, a different valve can be heard.

Chapter Review

The cardiac cycle comprises a complete relaxation and contraction of both the atria and ventricles, and lasts approximately 0.8 seconds. Beginning with all chambers in diastole, blood flows passively from the veins into the atria and past the atrioventricular valves into the ventricles. The atria begin to contract (atrial systole), following depolarization of the atria, and pump blood into the ventricles. The ventricles begin to contract (ventricular systole), raising pressure within the ventricles. When ventricular pressure rises above the pressure in the atria, blood flows toward the atria, producing the first heart sound, S_1 or lub. As pressure in the ventricles rises above two major arteries, blood pushes open the two semilunar valves and moves into the pulmonary trunk and aorta in the ventricular ejection phase. Following ventricular repolarization, the ventricles begin to relax (ventricular diastole), and pressure within the ventricles drops. As ventricular pressure drops, there is a tendency for blood to flow back into the atria from the major arteries, producing the dicrotic notch in the ECG and closing the two semilunar valves. The second heart sound, S_2 or dub, occurs when the semilunar valves close. When the pressure falls below that of the atria, blood moves from the atria into the ventricles, opening the atrioventricular valves and marking one complete heart cycle. The valves prevent backflow of blood. Failure of the valves to operate properly produces turbulent blood flow within the heart; the resulting heart murmur can often be heard with a stethoscope.

Review Questions

Exercise:

Problem:

The cardiac cycle consists of a distinct relaxation and contraction phase. Which term is typically used to refer ventricular contraction while no blood is being ejected?

a. systole
b. diastole
c. quiescent
d. isovolumic contraction

Solution:

D

Exercise:

Problem: Most blood enters the ventricle during _________.

a. atrial systole
b. atrial diastole
c. ventricular systole
d. isovolumic contraction

Solution:

B

Exercise:

Problem:

The first heart sound represents which portion of the cardiac cycle?

a. atrial systole
b. ventricular systole
c. closing of the atrioventricular valves

d. closing of the semilunar valves

Solution:

C

Exercise:

Problem: Ventricular relaxation immediately follows ________.

a. atrial depolarization
b. ventricular repolarization
c. ventricular depolarization
d. atrial repolarization

Solution:

B

Critical Thinking Questions

Exercise:

Problem:

Describe one cardiac cycle, beginning with both atria and ventricles relaxed.

Solution:

The cardiac cycle comprises a complete relaxation and contraction of both the atria and ventricles, and lasts approximately 0.8 seconds. Beginning with all chambers in diastole, blood flows passively from the veins into the atria and past the atrioventricular valves into the ventricles. The atria begin to contract following depolarization of the atria and pump blood into the ventricles. The ventricles begin to

contract, raising pressure within the ventricles. When ventricular pressure rises above the pressure in the two major arteries, blood pushes open the two semilunar valves and moves into the pulmonary trunk and aorta in the ventricular ejection phase. Following ventricular repolarization, the ventricles begin to relax, and pressure within the ventricles drops. When the pressure falls below that of the atria, blood moves from the atria into the ventricles, opening the atrioventricular valves and marking one complete heart cycle.

Glossary

cardiac cycle
: period of time between the onset of atrial contraction (atrial systole) and ventricular relaxation (ventricular diastole)

diastole
: period of time when the heart muscle is relaxed and the chambers fill with blood

end diastolic volume (EDV)
: (also, preload) the amount of blood in the ventricles at the end of atrial systole just prior to ventricular contraction

end systolic volume (ESV)
: amount of blood remaining in each ventricle following systole

heart sounds
: sounds heard via auscultation with a stethoscope of the closing of the atrioventricular valves (“lub”) and semilunar valves (“dub”)

isovolumic contraction
: (also, isovolumetric contraction) initial phase of ventricular contraction in which tension and pressure in the ventricle increase, but no blood is pumped or ejected from the heart

isovolumic ventricular relaxation phase

initial phase of the ventricular diastole when pressure in the ventricles drops below pressure in the two major arteries, the pulmonary trunk, and the aorta, and blood attempts to flow back into the ventricles, producing the dicrotic notch of the ECG and closing the two semilunar valves

murmur
: unusual heart sound detected by auscultation; typically related to septal or valve defects

preload
: (also, end diastolic volume) amount of blood in the ventricles at the end of atrial systole just prior to ventricular contraction

systole
: period of time when the heart muscle is contracting

ventricular ejection phase
: second phase of ventricular systole during which blood is pumped from the ventricle

Cardiac Physiology
By the end of this section, you will be able to:

- Relate heart rate to cardiac output
- Describe the effect of exercise on heart rate
- Identify cardiovascular centers and cardiac reflexes that regulate heart function
- Describe factors affecting heart rate
- Distinguish between positive and negative factors that affect heart contractility
- Summarize factors affecting stroke volume and cardiac output
- Describe the cardiac response to variations in blood flow and pressure

The autorhythmicity inherent in cardiac cells keeps the heart beating at a regular pace; however, the heart is regulated by and responds to outside influences as well. Neural and endocrine controls are vital to the regulation of cardiac function. In addition, the heart is sensitive to several environmental factors, including electrolytes.

Resting Cardiac Output

Cardiac output (CO) is a measurement of the amount of blood pumped by each ventricle in one minute. To calculate this value, multiply **stroke volume (SV)**, the amount of blood pumped by each ventricle, by **heart rate (HR)**, in contractions per minute (or beats per minute, bpm). It can be represented mathematically by the following equation:

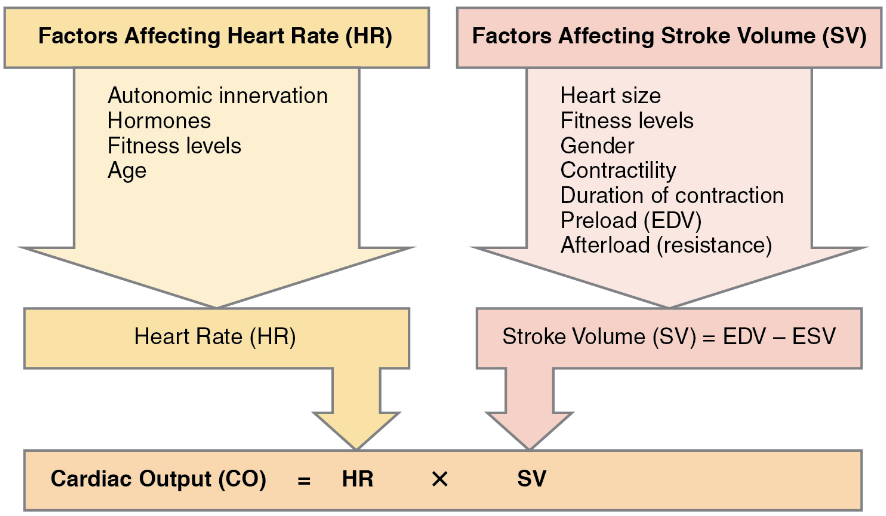
$$CO = HR \times SV$$

SV is normally measured using an echocardiogram to record EDV and ESV, and calculating the difference: SV = EDV – ESV. SV can also be measured using a specialized catheter, but this is an invasive procedure and far more dangerous to the patient. A mean SV for a resting 70-kg (150-lb) individual would be approximately 70 mL. There are several important variables, including size of the heart, physical and mental condition of the individual, sex, contractility, duration of contraction, preload or EDV, and afterload or resistance. Normal range for SV would be 55–100 mL. An average resting

HR would be approximately 75 bpm but could range from 60–100 in some individuals.

Using these numbers, the mean CO is 5.25 L/min, with a range of 4.0–8.0 L/min. Remember, however, that these numbers refer to CO from each ventricle separately, not the total for the heart. Factors influencing CO are summarized in [link].

Major Factors Influencing Cardiac Output



Cardiac output is influenced by heart rate and stroke volume, both of which are also variable.

SVs are also used to calculate **ejection fraction**, which is the portion of the blood that is pumped or ejected from the heart with each contraction. To calculate ejection fraction, SV is divided by EDV. Despite the name, the ejection fraction is normally expressed as a percentage. Ejection fractions range from approximately 55–70 percent, with a mean of 58 percent.

Exercise and Maximum Cardiac Output

In healthy young individuals, HR may increase to 150 bpm during exercise. SV can also increase from 70 to approximately 130 mL due to increased strength of contraction. This would increase CO to approximately 19.5

L/min, 4–5 times the resting rate. Top cardiovascular athletes can achieve even higher levels. At their peak performance, they may increase resting CO by 7–8 times.

Since the heart is a muscle, exercising it increases its efficiency. The difference between maximum and resting CO is known as the **cardiac reserve**. It measures the residual capacity of the heart to pump blood.

Heart Rates

HRs vary considerably, not only with exercise and fitness levels, but also with age. Newborn resting HRs may be 120 bpm. HR gradually decreases until young adulthood and then gradually increases again with age.

Maximum HRs are normally in the range of 200–220 bpm, although there are some extreme cases in which they may reach higher levels. As one ages, the ability to generate maximum rates decreases. This may be estimated by taking the maximal value of 220 bpm and subtracting the individual's age. So a 40-year-old individual would be expected to hit a maximum rate of approximately 180, and a 60-year-old person would achieve a HR of 160.

Note:
Disorders of the…
Heart: Abnormal Heart Rates
For an adult, normal resting HR will be in the range of 60–100 bpm. Bradycardia is the condition in which resting rate drops below 60 bpm, and tachycardia is the condition in which the resting rate is above 100 bpm. Trained athletes typically have very low HRs. If the patient is not exhibiting other symptoms, such as weakness, fatigue, dizziness, fainting, chest discomfort, palpitations, or respiratory distress, bradycardia is not considered clinically significant. However, if any of these symptoms are present, they may indicate that the heart is not providing sufficient oxygenated blood to the tissues. The term relative bradycardia may be used with a patient who has a HR in the normal range but is still suffering from

these symptoms. Most patients remain asymptomatic as long as the HR remains above 50 bpm.

Bradycardia may be caused by either inherent factors or causes external to the heart. While the condition may be inherited, typically it is acquired in older individuals. Inherent causes include abnormalities in either the SA or AV node. If the condition is serious, a pacemaker may be required. Other causes include ischemia to the heart muscle or diseases of the heart vessels or valves. External causes include metabolic disorders, pathologies of the endocrine system often involving the thyroid, electrolyte imbalances, neurological disorders including inappropriate autonomic responses, autoimmune pathologies, over-prescription of beta blocker drugs that reduce HR, recreational drug use, or even prolonged bed rest. Treatment relies upon establishing the underlying cause of the disorder and may necessitate supplemental oxygen.

Tachycardia is not normal in a resting patient but may be detected in pregnant women or individuals experiencing extreme stress. In the latter case, it would likely be triggered by stimulation from the limbic system or disorders of the autonomic nervous system. In some cases, tachycardia may involve only the atria. Some individuals may remain asymptomatic, but when present, symptoms may include dizziness, shortness of breath, lightheadedness, rapid pulse, heart palpations, chest pain, or fainting (syncope). While tachycardia is defined as a HR above 100 bpm, there is considerable variation among people. Further, the normal resting HRs of children are often above 100 bpm, but this is not considered to be tachycardia Many causes of tachycardia may be benign, but the condition may also be correlated with fever, anemia, hypoxia, hyperthyroidism, hypersecretion of catecholamines, some cardiomyopathies, some disorders of the valves, and acute exposure to radiation. Elevated rates in an exercising or resting patient are normal and expected. Resting rate should always be taken after recovery from exercise. Treatment depends upon the underlying cause but may include medications, implantable cardioverter defibrillators, ablation, or surgery.

Correlation Between Heart Rates and Cardiac Output

Initially, physiological conditions that cause HR to increase also trigger an increase in SV. During exercise, the rate of blood returning to the heart increases. However as the HR rises, there is less time spent in diastole and consequently less time for the ventricles to fill with blood. Even though there is less filling time, SV will initially remain high. However, as HR continues to increase, SV gradually decreases due to decreased filling time. CO will initially stabilize as the increasing HR compensates for the decreasing SV, but at very high rates, CO will eventually decrease as increasing rates are no longer able to compensate for the decreasing SV. Consider this phenomenon in a healthy young individual. Initially, as HR increases from resting to approximately 120 bpm, CO will rise. As HR increases from 120 to 160 bpm, CO remains stable, since the increase in rate is offset by decreasing ventricular filling time and, consequently, SV. As HR continues to rise above 160 bpm, CO actually decreases as SV falls faster than HR increases. So although aerobic exercises are critical to maintain the health of the heart, individuals are cautioned to monitor their HR to ensure they stay within the **target heart rate** range of between 120 and 160 bpm, so CO is maintained. The target HR is loosely defined as the range in which both the heart and lungs receive the maximum benefit from the aerobic workout and is dependent upon age.

Cardiovascular Centers

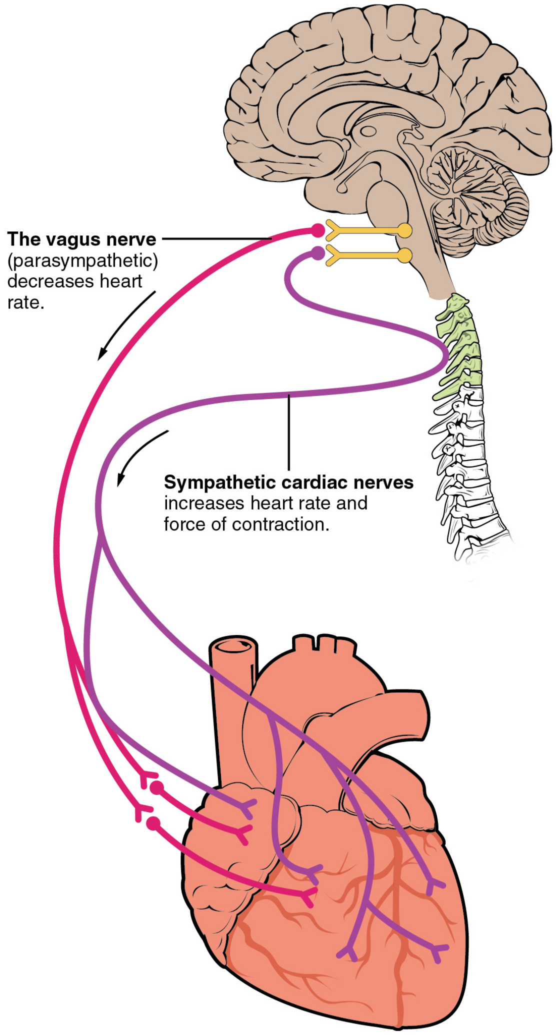
Nervous control over HR is centralized within the two paired cardiovascular centers of the medulla oblongata ([link]). The cardioaccelerator regions stimulate activity via sympathetic stimulation of the cardioaccelerator nerves, and the cardioinhibitory centers decrease heart activity via parasympathetic stimulation as one component of the vagus nerve, cranial nerve X. During rest, both centers provide slight stimulation to the heart, contributing to **autonomic tone**. This is a similar concept to tone in skeletal muscles. Normally, vagal stimulation predominates as, left unregulated, the SA node would initiate a sinus rhythm of approximately 100 bpm.

Both sympathetic and parasympathetic stimulations flow through a paired complex network of nerve fibers known as the **cardiac plexus** near the base of the heart. The cardioaccelerator center also sends additional fibers,

forming the cardiac nerves via sympathetic ganglia (the cervical ganglia plus superior thoracic ganglia T1–T4) to both the SA and AV nodes, plus additional fibers to the atria and ventricles. The ventricles are more richly innervated by sympathetic fibers than parasympathetic fibers. Sympathetic stimulation causes the release of the neurotransmitter norepinephrine (NE) at the neuromuscular junction of the cardiac nerves. NE shortens the repolarization period, thus speeding the rate of depolarization and contraction, which results in an increase in HR. It opens chemical- or ligand-gated sodium and calcium ion channels, allowing an influx of positively charged ions.

NE binds to the beta-1 receptor. Some cardiac medications (for example, beta blockers) work by blocking these receptors, thereby slowing HR and are one possible treatment for hypertension. Overprescription of these drugs may lead to bradycardia and even stoppage of the heart.

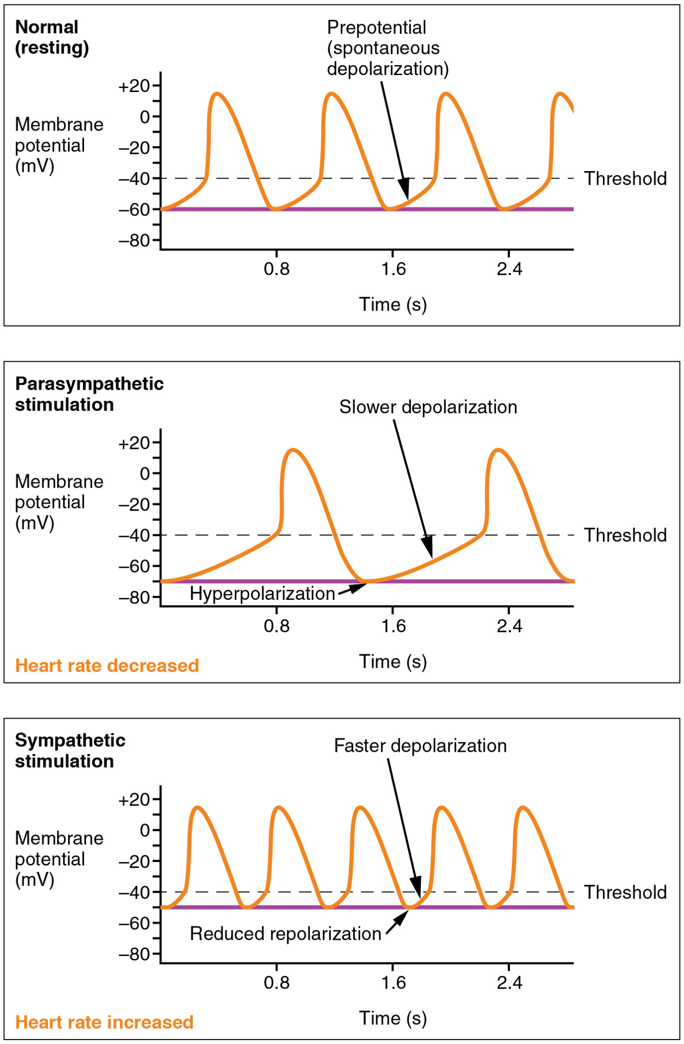
Autonomic Innervation of the Heart



Cardioaccelerator and cardioinhibitory areas are components of the paired cardiac centers located in the medulla oblongata of the brain. They innervate the heart via sympathetic cardiac nerves that increase cardiac activity and vagus (parasympathetic) nerves that slow cardiac activity.

Parasympathetic stimulation originates from the cardioinhibitory region with impulses traveling via the vagus nerve (cranial nerve X). The vagus nerve sends branches to both the SA and AV nodes, and to portions of both the atria and ventricles. Parasympathetic stimulation releases the neurotransmitter acetylcholine (ACh) at the neuromuscular junction. ACh slows HR by opening chemical- or ligand-gated potassium ion channels to slow the rate of spontaneous depolarization, which extends repolarization and increases the time before the next spontaneous depolarization occurs. Without any nervous stimulation, the SA node would establish a sinus rhythm of approximately 100 bpm. Since resting rates are considerably less than this, it becomes evident that parasympathetic stimulation normally slows HR. This is similar to an individual driving a car with one foot on the brake pedal. To speed up, one need merely remove one’s foot from the break and let the engine increase speed. In the case of the heart, decreasing parasympathetic stimulation decreases the release of ACh, which allows HR to increase up to approximately 100 bpm. Any increases beyond this rate would require sympathetic stimulation. [link] illustrates the effects of parasympathetic and sympathetic stimulation on the normal sinus rhythm.

Effects of Parasympathetic and Sympathetic Stimulation on Normal Sinus Rhythm



The wave of depolarization in a normal sinus rhythm shows a stable resting HR. Following parasympathetic stimulation, HR slows. Following sympathetic stimulation, HR increases.

Input to the Cardiovascular Center

The cardiovascular center receives input from a series of visceral receptors with impulses traveling through visceral sensory fibers within the vagus and

sympathetic nerves via the cardiac plexus. Among these receptors are various proprioreceptors, baroreceptors, and chemoreceptors, plus stimuli from the limbic system. Collectively, these inputs normally enable the cardiovascular centers to regulate heart function precisely, a process known as **cardiac reflexes**. Increased physical activity results in increased rates of firing by various proprioreceptors located in muscles, joint capsules, and tendons. Any such increase in physical activity would logically warrant increased blood flow. The cardiac centers monitor these increased rates of firing, and suppress parasympathetic stimulation and increase sympathetic stimulation as needed in order to increase blood flow.

Similarly, baroreceptors are stretch receptors located in the aortic sinus, carotid bodies, the venae cavae, and other locations, including pulmonary vessels and the right side of the heart itself. Rates of firing from the baroreceptors represent blood pressure, level of physical activity, and the relative distribution of blood. The cardiac centers monitor baroreceptor firing to maintain cardiac homeostasis, a mechanism called the **baroreceptor reflex**. With increased pressure and stretch, the rate of baroreceptor firing increases, and the cardiac centers decrease sympathetic stimulation and increase parasympathetic stimulation. As pressure and stretch decrease, the rate of baroreceptor firing decreases, and the cardiac centers increase sympathetic stimulation and decrease parasympathetic stimulation.

There is a similar reflex, called the **atrial reflex** or **Bainbridge reflex**, associated with varying rates of blood flow to the atria. Increased venous return stretches the walls of the atria where specialized baroreceptors are located. However, as the atrial baroreceptors increase their rate of firing and as they stretch due to the increased blood pressure, the cardiac center responds by increasing sympathetic stimulation and inhibiting parasympathetic stimulation to increase HR. The opposite is also true.

Increased metabolic byproducts associated with increased activity, such as carbon dioxide, hydrogen ions, and lactic acid, plus falling oxygen levels, are detected by a suite of chemoreceptors innervated by the glossopharyngeal and vagus nerves. These chemoreceptors provide

feedback to the cardiovascular centers about the need for increased or decreased blood flow, based on the relative levels of these substances.

The limbic system can also significantly impact HR related to emotional state. During periods of stress, it is not unusual to identify higher than normal HRs, often accompanied by a surge in the stress hormone cortisol. Individuals experiencing extreme anxiety may manifest panic attacks with symptoms that resemble those of heart attacks. These events are typically transient and treatable. Meditation techniques have been developed to ease anxiety and have been shown to lower HR effectively. Doing simple deep and slow breathing exercises with one's eyes closed can also significantly reduce this anxiety and HR.

Note:

Disorders of the…

Heart: Broken Heart Syndrome

Extreme stress from such life events as the death of a loved one, an emotional break up, loss of income, or foreclosure of a home may lead to a condition commonly referred to as broken heart syndrome. This condition may also be called Takotsubo cardiomyopathy, transient apical ballooning syndrome, apical ballooning cardiomyopathy, stress-induced cardiomyopathy, Gebrochenes-Herz syndrome, and stress cardiomyopathy. The recognized effects on the heart include congestive heart failure due to a profound weakening of the myocardium not related to lack of oxygen. This may lead to acute heart failure, lethal arrhythmias, or even the rupture of a ventricle. The exact etiology is not known, but several factors have been suggested, including transient vasospasm, dysfunction of the cardiac capillaries, or thickening of the myocardium—particularly in the left ventricle—that may lead to the critical circulation of blood to this region. While many patients survive the initial acute event with treatment to restore normal function, there is a strong correlation with death. Careful statistical analysis by the Cass Business School, a prestigious institution located in London, published in 2008, revealed that within one year of the death of a loved one, women are more than twice as likely to die and males are six times as likely to die as would otherwise be expected.

Other Factors Influencing Heart Rate

Using a combination of autorhythmicity and innervation, the cardiovascular center is able to provide relatively precise control over HR. However, there are a number of other factors that have an impact on HR as well, including epinephrine, NE, and thyroid hormones; levels of various ions including calcium, potassium, and sodium; body temperature; hypoxia; and pH balance ([link] and [link]). After reading this section, the importance of maintaining homeostasis should become even more apparent.

Major Factors Increasing Heart Rate and Force of Contraction	
Factor	**Effect**
Cardioaccelerator nerves	Release of norepinephrine by cardioaccelerator nerves
Proprioreceptors	Increased firing rates of proprioreceptors (e.g. during exercise)
Chemoreceptors	Chemoreceptors sensing decreased levels of O_2 or increased levels of H^+, CO_2 and lactic acid
Baroreceptors	Decreased firing rates of baroreceptors (indicating falling blood volume/pressure)
Limbic system	Anticipation of physical exercise or strong emotions by the limbic system
Catecholamines	Increased epinephrine and norepinephrine release by the adrenal glands

Major Factors Increasing Heart Rate and Force of Contraction	
Factor	**Effect**
Thyroid hormones	Increased T_3 and T_4 in the blood (released by thyroid)
Calcium	Increase in calcium ions in the blood
Potassium	Decrease in potassium ions in the blood
Sodium	Decrease in sodium ions in the blood
Body temperature	Increase in body temperature
Nicotine and caffeine	Presence of nicotine, caffeine or other stimulants

Factors Decreasing Heart Rate and Force of Contraction	
Factor	**Effect**
Cardioinhibitor nerves (vagus)	Release of acetylcholine by cardioaccelerator nerves
Proprioreceptors	Decreased firing rates of proprioreceptors (e.g. during rest)
Chemoreceptors	Chemoreceptors sensing increased levels of O_2 or decreased levels of H^+, CO_2 and lactic acid

Factors Decreasing Heart Rate and Force of Contraction	
Factor	**Effect**
Baroreceptors	Increased firing rates of baroreceptors (indicating rising blood volume/pressure)
Limbic system	Anticipation of relaxation by the limbic system
Catecholamines	Increased epinephrine and norepinephrine release by the adrenal glands
Thyroid hormones	Decreased T_3 and T_4 in the blood (released by thyroid)
Calcium	Increase in calcium ions in the blood
Potassium	Increase in potassium ions in the blood
Sodium	Increase in sodium ions in the blood
Body temperature	Decrease in body temperature
Opiates and tranquilizers	Presence of opiates (heroin), tranquilizers or other depressants

Epinephrine and Norepinephrine

The catecholamines, epinephrine and NE, secreted by the adrenal medulla form one component of the extended fight-or-flight mechanism. The other component is sympathetic stimulation. Epinephrine and NE have similar effects: binding to the beta-1 receptors, and opening sodium and calcium ion chemical- or ligand-gated channels. The rate of depolarization is increased by this additional influx of positively charged ions, so the

threshold is reached more quickly and the period of repolarization is shortened. However, massive releases of these hormones coupled with sympathetic stimulation may actually lead to arrhythmias. There is no parasympathetic stimulation to the adrenal medulla.

Thyroid Hormones

In general, increased levels of thyroid hormone, or thyroxin, increase cardiac rate and contractility. The impact of thyroid hormone is typically of a much longer duration than that of the catecholamines. The physiologically active form of thyroid hormone, T_3 or triiodothyronine, has been shown to directly enter cardiomyocytes and alter activity at the level of the genome. It also impacts the beta adrenergic response similar to epinephrine and NE described above. Excessive levels of thyroxin may trigger tachycardia.

Calcium

Calcium ion levels have great impacts upon both HR and contractility; as the levels of calcium ions increase, so do HR and contractility. High levels of calcium ions (hypercalcemia) may be implicated in a short QT interval and a widened T wave in the ECG. The QT interval represents the time from the start of depolarization to repolarization of the ventricles, and includes the period of ventricular systole. Extremely high levels of calcium may induce cardiac arrest. Drugs known as calcium channel blockers slow HR by binding to these channels and blocking or slowing the inward movement of calcium ions.

Caffeine and Nicotine

Caffeine and nicotine are not found naturally within the body. Both of these nonregulated drugs have an excitatory effect on membranes of neurons in general and have a stimulatory effect on the cardiac centers specifically, causing an increase in HR. Caffeine works by increasing the rates of

depolarization at the SA node, whereas nicotine stimulates the activity of the sympathetic neurons that deliver impulses to the heart.

Although it is the world’s most widely consumed psychoactive drug, caffeine is legal and not regulated. While precise quantities have not been established, “normal” consumption is not considered harmful to most people, although it may cause disruptions to sleep and acts as a diuretic. Its consumption by pregnant women is cautioned against, although no evidence of negative effects has been confirmed. Tolerance and even physical and mental addiction to the drug result in individuals who routinely consume the substance.

Nicotine, too, is a stimulant and produces addiction. While legal and nonregulated, concerns about nicotine’s safety and documented links to respiratory and cardiac disease have resulted in warning labels on cigarette packages.

Factors Decreasing Heart Rate

HR can be slowed when a person experiences altered sodium and potassium levels, hypoxia, acidosis, alkalosis, and hypothermia (see [link]). The relationship between electrolytes and HR is complex, but maintaining electrolyte balance is critical to the normal wave of depolarization. Of the two ions, potassium has the greater clinical significance. Initially, both hyponatremia (low sodium levels) and hypernatremia (high sodium levels) may lead to tachycardia. Severely high hypernatremia may lead to fibrillation, which may cause CO to cease. Severe hyponatremia leads to both bradycardia and other arrhythmias. Hypokalemia (low potassium levels) also leads to arrhythmias, whereas hyperkalemia (high potassium levels) causes the heart to become weak and flaccid, and ultimately to fail.

Acidosis is a condition in which excess hydrogen ions are present, and the patient’s blood expresses a low pH value. Alkalosis is a condition in which there are too few hydrogen ions, and the patient’s blood has an elevated pH. Normal blood pH falls in the range of 7.35–7.45, so a number lower than this range represents acidosis and a higher number represents alkalosis.

Recall that enzymes are the regulators or catalysts of virtually all biochemical reactions; they are sensitive to pH and will change shape slightly with values outside their normal range. These variations in pH and accompanying slight physical changes to the active site on the enzyme decrease the rate of formation of the enzyme-substrate complex, subsequently decreasing the rate of many enzymatic reactions, which can have complex effects on HR. Severe changes in pH will lead to denaturation of the enzyme.

The last variable is body temperature. Elevated body temperature is called hyperthermia, and suppressed body temperature is called hypothermia. Slight hyperthermia results in increasing HR and strength of contraction. Hypothermia slows the rate and strength of heart contractions. This distinct slowing of the heart is one component of the larger diving reflex that diverts blood to essential organs while submerged. If sufficiently chilled, the heart will stop beating, a technique that may be employed during open heart surgery. In this case, the patient's blood is normally diverted to an artificial heart-lung machine to maintain the body's blood supply and gas exchange until the surgery is complete, and sinus rhythm can be restored. Excessive hyperthermia and hypothermia will both result in death, as enzymes drive the body systems to cease normal function, beginning with the central nervous system.

Stroke Volume

Many of the same factors that regulate HR also impact cardiac function by altering SV. While a number of variables are involved, SV is ultimately dependent upon the difference between EDV and ESV. The three primary factors to consider are preload, or the stretch on the ventricles prior to contraction; the contractility, or the force or strength of the contraction itself; and afterload, the force the ventricles must generate to pump blood against the resistance in the vessels. These factors are summarized in [link] and [link].

Preload

Preload is another way of expressing EDV. Therefore, the greater the EDV is, the greater the preload is. One of the primary factors to consider is **filling time**, or the duration of ventricular diastole during which filling occurs. The more rapidly the heart contracts, the shorter the filling time becomes, and the lower the EDV and preload are. This effect can be partially overcome by increasing the second variable, contractility, and raising SV, but over time, the heart is unable to compensate for decreased filling time, and preload also decreases.

With increasing ventricular filling, both EDV or preload increase, and the cardiac muscle itself is stretched to a greater degree. At rest, there is little stretch of the ventricular muscle, and the sarcomeres remain short. With increased ventricular filling, the ventricular muscle is increasingly stretched and the sarcomere length increases. As the sarcomeres reach their optimal lengths, they will contract more powerfully, because more of the myosin heads can bind to the actin on the thin filaments, forming cross bridges and increasing the strength of contraction and SV. If this process were to continue and the sarcomeres stretched beyond their optimal lengths, the force of contraction would decrease. However, due to the physical constraints of the location of the heart, this excessive stretch is not a concern.

The relationship between ventricular stretch and contraction has been stated in the well-known **Frank-Starling mechanism** or simply Starling’s Law of the Heart. This principle states that, within physiological limits, the force of heart contraction is directly proportional to the initial length of the muscle fiber. This means that the greater the stretch of the ventricular muscle (within limits), the more powerful the contraction is, which in turn increases SV. Therefore, by increasing preload, you increase the second variable, contractility.

Otto Frank (1865–1944) was a German physiologist; among his many published works are detailed studies of this important heart relationship. Ernest Starling (1866–1927) was an important English physiologist who also studied the heart. Although they worked largely independently, their combined efforts and similar conclusions have been recognized in the name “Frank-Starling mechanism.”

Any sympathetic stimulation to the venous system will increase venous return to the heart, which contributes to ventricular filling, and EDV and preload. While much of the ventricular filling occurs while both atria and ventricles are in diastole, the contraction of the atria, the atrial kick, plays a crucial role by providing the last 20–30 percent of ventricular filling.

Contractility

It is virtually impossible to consider preload or ESV without including an early mention of the concept of contractility. Indeed, the two parameters are intimately linked. Contractility refers to the force of the contraction of the heart muscle, which controls SV, and is the primary parameter for impacting ESV. The more forceful the contraction is, the greater the SV and smaller the ESV are. Less forceful contractions result in smaller SVs and larger ESVs. Factors that increase contractility are described as **positive inotropic factors**, and those that decrease contractility are described as **negative inotropic factors** (ino- = “fiber;” -tropic = “turning toward”).

Not surprisingly, sympathetic stimulation is a positive inotrope, whereas parasympathetic stimulation is a negative inotrope. Sympathetic stimulation triggers the release of NE at the neuromuscular junction from the cardiac nerves and also stimulates the adrenal cortex to secrete epinephrine and NE. In addition to their stimulatory effects on HR, they also bind to both alpha and beta receptors on the cardiac muscle cell membrane to increase metabolic rate and the force of contraction. This combination of actions has the net effect of increasing SV and leaving a smaller residual ESV in the ventricles. In comparison, parasympathetic stimulation releases ACh at the neuromuscular junction from the vagus nerve. The membrane hyperpolarizes and inhibits contraction to decrease the strength of contraction and SV, and to raise ESV. Since parasympathetic fibers are more widespread in the atria than in the ventricles, the primary site of action is in the upper chambers. Parasympathetic stimulation in the atria decreases the atrial kick and reduces EDV, which decreases ventricular stretch and preload, thereby further limiting the force of ventricular contraction. Stronger parasympathetic stimulation also directly decreases the force of contraction of the ventricles.

Several synthetic drugs, including dopamine and isoproterenol, have been developed that mimic the effects of epinephrine and NE by stimulating the influx of calcium ions from the extracellular fluid. Higher concentrations of intracellular calcium ions increase the strength of contraction. Excess calcium (hypercalcemia) also acts as a positive inotropic agent. The drug digitalis lowers HR and increases the strength of the contraction, acting as a positive inotropic agent by blocking the sequestering of calcium ions into the sarcoplasmic reticulum. This leads to higher intracellular calcium levels and greater strength of contraction. In addition to the catecholamines from the adrenal medulla, other hormones also demonstrate positive inotropic effects. These include thyroid hormones and glucagon from the pancreas.

Negative inotropic agents include hypoxia, acidosis, hyperkalemia, and a variety of synthetic drugs. These include numerous beta blockers and calcium channel blockers. Early beta blocker drugs include propranolol and pronethalol, and are credited with revolutionizing treatment of cardiac patients experiencing angina pectoris. There is also a large class of dihydropyridine, phenylalkylamine, and benzothiazepine calcium channel blockers that may be administered decreasing the strength of contraction and SV.

Afterload

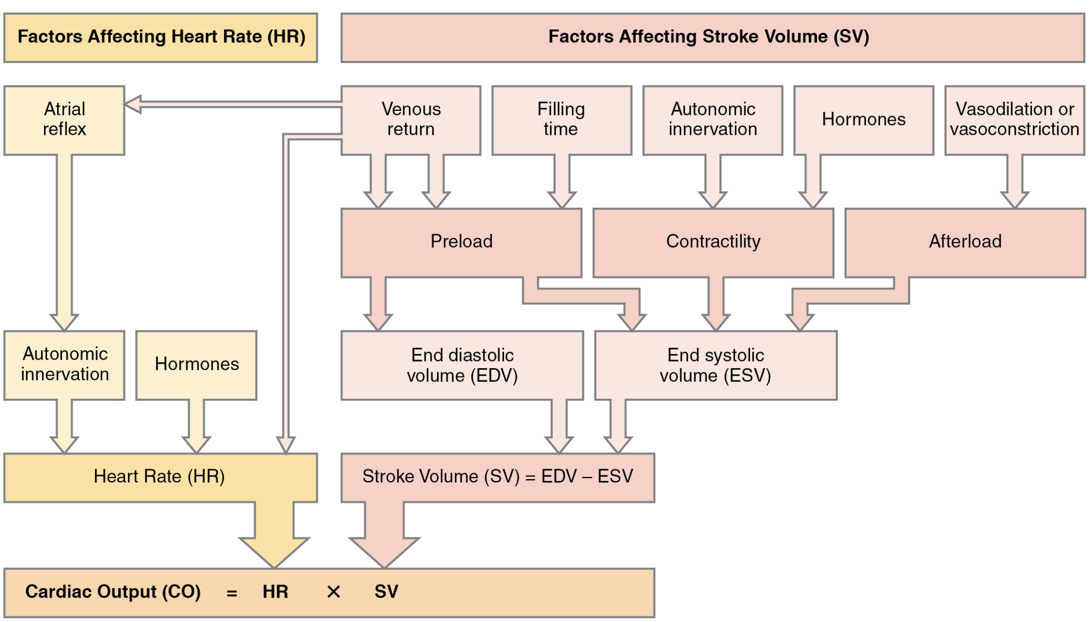
Afterload refers to the tension that the ventricles must develop to pump blood effectively against the resistance in the vascular system. Any condition that increases resistance requires a greater afterload to force open the semilunar valves and pump the blood. Damage to the valves, such as stenosis, which makes them harder to open will also increase afterload. Any decrease in resistance decreases the afterload. [link] summarizes the major factors influencing SV, [link] summarizes the major factors influencing CO, and [link] and [link] summarize cardiac responses to increased and decreased blood flow and pressure in order to restore homeostasis.

Major Factors Influencing Stroke Volume

	Factors Affecting Stroke Volume (SV)		
	Preload	**Contractility**	**Afterload**
Raised due to:	• fast filling time • increased venous return **Increases end diastolic volume,** **Increases stroke volume**	• sympathetic stimulation • epinephrine and norepinephrine • high intracellular calcium ions • high blood calcium level • thyroid hormones • glucagon **Decreases end systolic volume,** **Increases stroke volume**	• increased vascular resistance • semilunar valve damage **Increases end systolic volume** **Decreases stroke volume**
Lowered due to:	• decreased thyroid hormones • decreased calcium ions • high or low potassium ions • high or low sodium • low body temperature • hypoxia • abnormal pH balance • drugs (i.e., calcium channel blockers) **Decreases end diastolic volume,** **Decreases stroke volume**	• parasympathetic stimulation • acetylcholine • hypoxia • hyperkalemia **Increases end systolic volume** **Decreases stroke volume**	• decreased vascular resistance **Decreases end systolic volume** **Increases stroke volume**

Multiple factors impact preload, afterload, and contractility, and are the major considerations influencing SV.

Summary of Major Factors Influencing Cardiac Output



The primary factors influencing HR include autonomic innervation plus endocrine control. Not shown are environmental factors, such as electrolytes, metabolic products,

and temperature. The primary factors controlling SV include preload, contractility, and afterload. Other factors such as electrolytes may be classified as either positive or negative inotropic agents.

Cardiac Response to Decreasing Blood Flow and Pressure Due to Decreasing Cardiac Output		
	Baroreceptors (aorta, carotid arteries, venae cavae, and atria)	**Chemoreceptors (both central nervous system and in proximity to baroreceptors)**
Sensitive to	Decreasing stretch	Decreasing O_2 and increasing CO_2, H^+, and lactic acid
Target	Parasympathetic stimulation suppressed	Sympathetic stimulation increased
Response of heart	Increasing heart rate and increasing stroke volume	Increasing heart rate and increasing stroke volume
Overall effect	Increasing blood flow and pressure due to increasing cardiac output; hemostasis restored	Increasing blood flow and pressure due to increasing cardiac output; hemostasis restored

Cardiac Response to Increasing Blood Flow and Pressure Due to Increasing Cardiac Output		
	Baroreceptors (aorta, carotid arteries, venae cavae, and atria)	**Chemoreceptors (both central nervous system and in proximity to baroreceptors)**
Sensitive to	Increasing stretch	Increasing O_2 and decreasing CO_2, H^+, and lactic acid
Target	Parasympathetic stimulation increased	Sympathetic stimulation suppressed
Response of heart	Decreasing heart rate and decreasing stroke volume	Decreasing heart rate and decreasing stroke volume
Overall effect	Decreasing blood flow and pressure due to decreasing cardiac output; hemostasis restored	Decreasing blood flow and pressure due to decreasing cardiac output; hemostasis restored

Chapter Review

Many factors affect HR and SV, and together, they contribute to cardiac function. HR is largely determined and regulated by autonomic stimulation and hormones. There are several feedback loops that contribute to maintaining homeostasis dependent upon activity levels, such as the atrial reflex, which is determined by venous return.

SV is regulated by autonomic innervation and hormones, but also by filling time and venous return. Venous return is determined by activity of the skeletal muscles, blood volume, and changes in peripheral circulation.

Venous return determines preload and the atrial reflex. Filling time directly related to HR also determines preload. Preload then impacts both EDV and ESV. Autonomic innervation and hormones largely regulate contractility. Contractility impacts EDV as does afterload. CO is the product of HR multiplied by SV. SV is the difference between EDV and ESV.

Review Questions

Exercise:

Problem:

The force the heart must overcome to pump blood is known as ________.

a. preload
b. afterload
c. cardiac output
d. stroke volume

Solution:

B

Exercise:

Problem:

The cardiovascular centers are located in which area of the brain?

a. medulla oblongata
b. pons
c. mesencephalon (midbrain)
d. cerebrum

Solution:

A

Exercise:

Problem:

In a healthy young adult, what happens to cardiac output when heart rate increases above 160 bpm?

a. It increases.
b. It decreases.
c. It remains constant.
d. There is no way to predict.

Solution:

B

Exercise:

Problem:

What happens to preload when there is venous constriction in the veins?

a. It increases.
b. It decreases.
c. It remains constant.
d. There is no way to predict.

Solution:

A

Exercise:

Problem: Which of the following is a positive inotrope?

a. Na^+

b. K^+
c. Ca^{2+}
d. both Na^+ and K^+

Solution:

C

Critical Thinking Questions

Exercise:

Problem: Why does increasing EDV increase contractility?

Solution:

Increasing EDV increases the sarcomeres’ lengths within the cardiac muscle cells, allowing more cross bridge formation between the myosin and actin and providing for a more powerful contraction. This relationship is described in the Frank-Starling mechanism.

Exercise:

Problem: Why is afterload important to cardiac function?

Solution:

Afterload represents the resistance within the arteries to the flow of blood ejected from the ventricles. If uncompensated, if afterload increases, flow will decrease. In order for the heart to maintain adequate flow to overcome increasing afterload, it must pump more forcefully. This is one of the negative consequences of high blood pressure or hypertension.

Glossary

afterload

force the ventricles must develop to effectively pump blood against the resistance in the vessels

autonomic tone

contractile state during resting cardiac activity produced by mild sympathetic and parasympathetic stimulation

atrial reflex

(also, called Bainbridge reflex) autonomic reflex that responds to stretch receptors in the atria that send impulses to the cardioaccelerator area to increase HR when venous flow into the atria increases

Bainbridge reflex

(also, called atrial reflex) autonomic reflex that responds to stretch receptors in the atria that send impulses to the cardioaccelerator area to increase HR when venous flow into the atria increases

baroreceptor reflex

autonomic reflex in which the cardiac centers monitor signals from the baroreceptor stretch receptors and regulate heart function based on blood flow

cardiac output (CO)

amount of blood pumped by each ventricle during one minute; equals HR multiplied by SV

cardiac plexus

paired complex network of nerve fibers near the base of the heart that receive sympathetic and parasympathetic stimulations to regulate HR

cardiac reflexes

series of autonomic reflexes that enable the cardiovascular centers to regulate heart function based upon sensory information from a variety of visceral sensors

cardiac reserve

difference between maximum and resting CO

ejection fraction

portion of the blood that is pumped or ejected from the heart with each contraction; mathematically represented by SV divided by EDV

filling time

duration of ventricular diastole during which filling occurs

Frank-Starling mechanism

relationship between ventricular stretch and contraction in which the force of heart contraction is directly proportional to the initial length of the muscle fiber

heart rate (HR)

number of times the heart contracts (beats) per minute

negative inotropic factors

factors that negatively impact or lower heart contractility

positive inotropic factors

factors that positively impact or increase heart contractility

stroke volume (SV)

amount of blood pumped by each ventricle per contraction; also, the difference between EDV and ESV

target heart rate

range in which both the heart and lungs receive the maximum benefit from an aerobic workout

Structure and Function of Blood Vessels

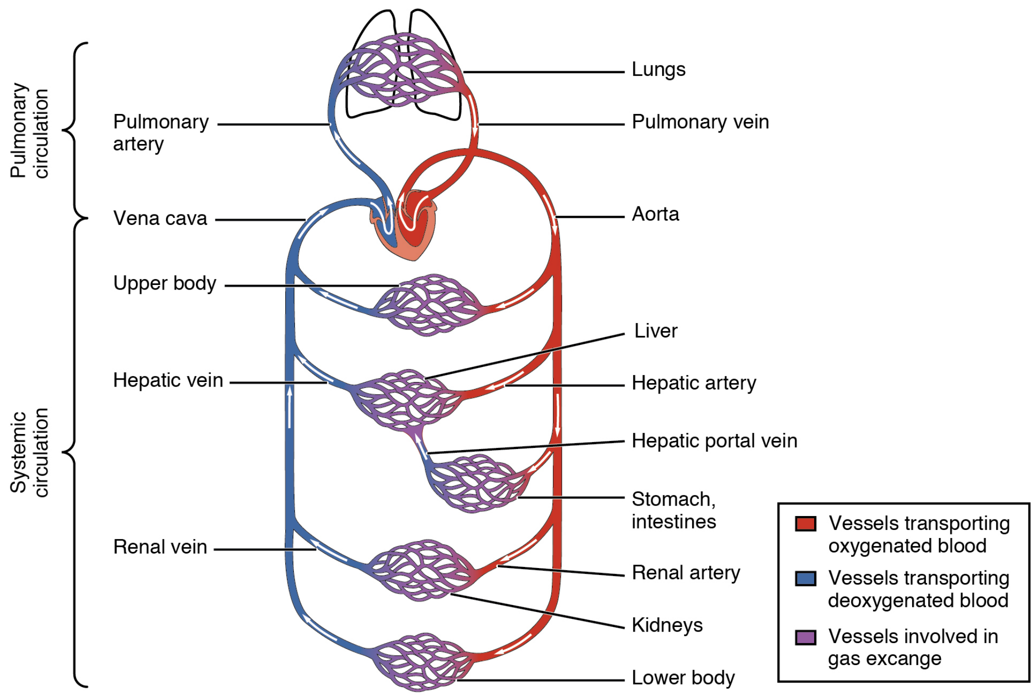
By the end of this section, you will be able to:

- Compare and contrast the three tunics that make up the walls of most blood vessels
- Distinguish between elastic arteries, muscular arteries, and arterioles on the basis of structure, location, and function
- Describe the basic structure of a capillary bed, from the supplying metarteriole to the venule into which it drains
- Explain the structure and function of venous valves in the large veins of the extremities

Blood is carried through the body via blood vessels. An artery is a blood vessel that carries blood away from the heart, where it branches into ever-smaller vessels. Eventually, the smallest arteries, vessels called arterioles, further branch into tiny capillaries, where nutrients and wastes are exchanged, and then combine with other vessels that exit capillaries to form venules, small blood vessels that carry blood to a vein, a larger blood vessel that returns blood to the heart.

Arteries and veins transport blood in two distinct circuits: the systemic circuit and the pulmonary circuit ([link]). Systemic arteries provide blood rich in oxygen to the body's tissues. The blood returned to the heart through systemic veins has less oxygen, since much of the oxygen carried by the arteries has been delivered to the cells. In contrast, in the pulmonary circuit, arteries carry blood low in oxygen exclusively to the lungs for gas exchange. Pulmonary veins then return freshly oxygenated blood from the lungs to the heart to be pumped back out into systemic circulation. Although arteries and veins differ structurally and functionally, they share certain features.

Cardiovascular Circulation



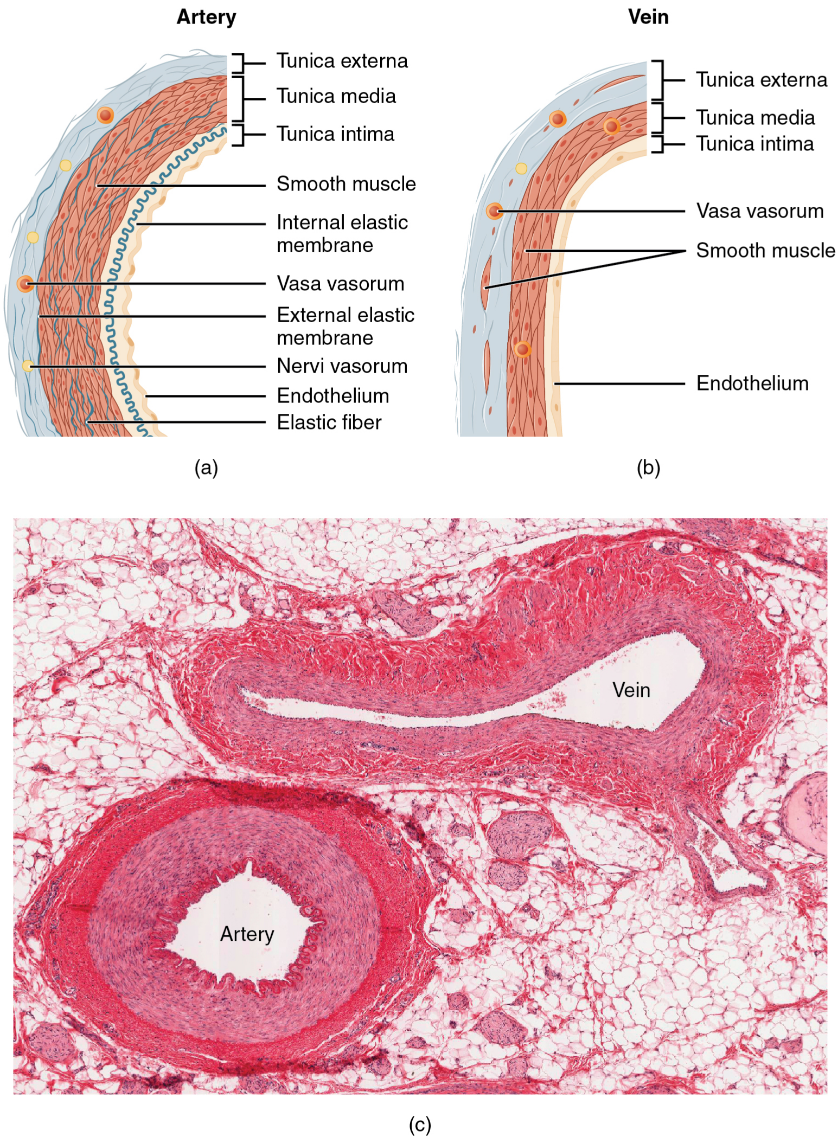
The pulmonary circuit moves blood from the right side of the heart to the lungs and back to the heart. The systemic circuit moves blood from the left side of the heart to the head and body and returns it to the right side of the heart to repeat the cycle. The arrows indicate the direction of blood flow, and the colors show the relative levels of oxygen concentration.

Shared Structures

Different types of blood vessels vary slightly in their structures, but they share the same general features. Arteries and arterioles have thicker walls than veins and venules because they are closer to the heart and receive blood that is surging at a far greater pressure ([link]). Each type of vessel has a **lumen**—a hollow passageway through which blood flows. Arteries have smaller lumens than veins, a characteristic that helps to maintain the pressure of blood moving through the system. Together, their thicker walls

and smaller diameters give arterial lumens a more rounded appearance in cross section than the lumens of veins.

Structure of Blood Vessels



(a) Arteries and (b) veins share the same general features, but the walls of arteries are much thicker because of the higher pressure of the blood that flows through them. (c) A micrograph shows the relative differences in thickness. LM × 160. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

By the time blood has passed through capillaries and entered venules, the pressure initially exerted upon it by heart contractions has diminished. In other words, in comparison to arteries, venules and veins withstand a much lower pressure from the blood that flows through them. Their walls are considerably thinner and their lumens are correspondingly larger in diameter, allowing more blood to flow with less vessel resistance. In addition, many veins of the body, particularly those of the limbs, contain valves that assist the unidirectional flow of blood toward the heart. This is critical because blood flow becomes sluggish in the extremities, as a result of the lower pressure and the effects of gravity.

The walls of arteries and veins are largely composed of living cells and their products (including collagenous and elastic fibers); the cells require nourishment and produce waste. Since blood passes through the larger vessels relatively quickly, there is limited opportunity for blood in the lumen of the vessel to provide nourishment to or remove waste from the vessel's cells. Further, the walls of the larger vessels are too thick for nutrients to diffuse through to all of the cells. Larger arteries and veins contain small blood vessels within their walls known as the **vasa vasorum**—literally "vessels of the vessel"—to provide them with this critical exchange. Since the pressure within arteries is relatively high, the vasa vasorum must function in the outer layers of the vessel (see [link]) or the pressure exerted by the blood passing through the vessel would collapse it, preventing any exchange from occurring. The lower pressure within veins allows the vasa vasorum to be located closer to the lumen. The restriction of the vasa vasorum to the outer layers of arteries is thought to be one reason that arterial diseases are more common than venous diseases, since its location makes it more difficult to nourish the cells of the arteries and remove waste products. There are also minute nerves within the walls of both types of vessels that control the contraction and dilation of smooth muscle. These minute nerves are known as the nervi vasorum.

Both arteries and veins have the same three distinct tissue layers, called tunics (from the Latin term tunica), for the garments first worn by ancient Romans; the term tunic is also used for some modern garments. From the

most interior layer to the outer, these tunics are the tunica intima, the tunica media, and the tunica externa (see [link]). [link] compares and contrasts the tunics of the arteries and veins.

Comparison of Tunics in Arteries and Veins		
	Arteries	**Veins**
General appearance	Thick walls with small lumens Generally appear rounded	Thin walls with large lumens Generally appear flattened
Tunica intima	Endothelium usually appears wavy due to constriction of smooth muscle Internal elastic membrane present in larger vessels	Endothelium appears smooth Internal elastic membrane absent

Comparison of Tunics in Arteries and Veins		
	Arteries	**Veins**
Tunica media	Normally the thickest layer in arteries Smooth muscle cells and elastic fibers predominate (the proportions of these vary with distance from the heart) External elastic membrane present in larger vessels	Normally thinner than the tunica externa Smooth muscle cells and collagenous fibers predominate Nervi vasorum and vasa vasorum present External elastic membrane absent
Tunica externa	Normally thinner than the tunica media in all but the largest arteries Collagenous and elastic fibers Nervi vasorum and vasa vasorum present	Normally the thickest layer in veins Collagenous and smooth fibers predominate Some smooth muscle fibers Nervi vasorum and vasa vasorum present

Tunica Intima

The **tunica intima** (also called the tunica interna) is composed of epithelial and connective tissue layers. Lining the tunica intima is the specialized simple squamous epithelium called the endothelium, which is continuous throughout the entire vascular system, including the lining of the chambers of the heart. Damage to this endothelial lining and exposure of blood to the collagenous fibers beneath is one of the primary causes of clot formation. Until recently, the endothelium was viewed simply as the boundary between the blood in the lumen and the walls of the vessels. Recent studies, however, have shown that it is physiologically critical to such activities as helping to regulate capillary exchange and altering blood flow. The endothelium releases local chemicals called endothelins that can constrict the smooth muscle within the walls of the vessel to increase blood pressure. Uncompensated overproduction of endothelins may contribute to hypertension (high blood pressure) and cardiovascular disease.

Next to the endothelium is the basement membrane, or basal lamina, that effectively binds the endothelium to the connective tissue. The basement membrane provides strength while maintaining flexibility, and it is permeable, allowing materials to pass through it. The thin outer layer of the tunica intima contains a small amount of areolar connective tissue that consists primarily of elastic fibers to provide the vessel with additional flexibility; it also contains some collagenous fibers to provide additional strength.

In larger arteries, there is also a thick, distinct layer of elastic fibers known as the **internal elastic membrane** (also called the internal elastic lamina) at the boundary with the tunica media. Like the other components of the tunica intima, the internal elastic membrane provides structure while allowing the vessel to stretch. It is permeated with small openings that allow exchange of materials between the tunics. The internal elastic membrane is not apparent in veins. In addition, many veins, particularly in the lower limbs, contain valves formed by sections of thickened endothelium that are reinforced with connective tissue, extending into the lumen.

Under the microscope, the lumen and the entire tunica intima of a vein will appear smooth, whereas those of an artery will normally appear wavy because of the partial constriction of the smooth muscle in the tunica media, the next layer of blood vessel walls.

Tunica Media

The **tunica media** is the substantial middle layer of the vessel wall (see [link]). It is generally the thickest layer in arteries, and it is much thicker in arteries than it is in veins. The tunica media consists of layers of smooth muscle supported by connective tissue that is primarily made up of elastic fibers, most of which are arranged in circular sheets. Toward the outer portion of the tunic, there are also layers of longitudinal muscle. Contraction and relaxation of the circular muscles decrease and increase the diameter of the vessel lumen, respectively. Specifically in arteries, **vasoconstriction** decreases blood flow as the smooth muscle in the walls of the tunica media contracts, making the lumen narrower and increasing blood pressure. Similarly, **vasodilation** increases blood flow as the smooth muscle relaxes, allowing the lumen to widen and blood pressure to drop. Both vasoconstriction and vasodilation are regulated in part by small vascular nerves, known as **nervi vasorum**, or “nerves of the vessel,” that run within the walls of blood vessels. These are generally all sympathetic fibers, although some trigger vasodilation and others induce vasoconstriction, depending upon the nature of the neurotransmitter and receptors located on the target cell. Parasympathetic stimulation does trigger vasodilation as well as erection during sexual arousal in the external genitalia of both sexes. Nervous control over vessels tends to be more generalized than the specific targeting of individual blood vessels. Local controls, discussed later, account for this phenomenon. (Seek additional content for more information on these dynamic aspects of the autonomic nervous system.) Hormones and local chemicals also control blood vessels. Together, these neural and chemical mechanisms reduce or increase blood flow in response to changing body conditions, from exercise to hydration. Regulation of both blood flow and blood pressure is discussed in detail later in this chapter.

The smooth muscle layers of the tunica media are supported by a framework of collagenous fibers that also binds the tunica media to the inner and outer tunics. Along with the collagenous fibers are large numbers of elastic fibers that appear as wavy lines in prepared slides. Separating the tunica media from the outer tunica externa in larger arteries is the **external elastic membrane** (also called the external elastic lamina), which also appears wavy in slides. This structure is not usually seen in smaller arteries, nor is it seen in veins.

Tunica Externa

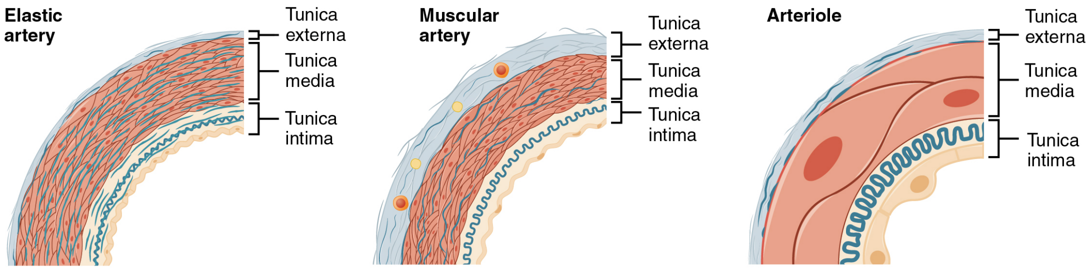
The outer tunic, the **tunica externa** (also called the tunica adventitia), is a substantial sheath of connective tissue composed primarily of collagenous fibers. Some bands of elastic fibers are found here as well. The tunica externa in veins also contains groups of smooth muscle fibers. This is normally the thickest tunic in veins and may be thicker than the tunica media in some larger arteries. The outer layers of the tunica externa are not distinct but rather blend with the surrounding connective tissue outside the vessel, helping to hold the vessel in relative position. If you are able to palpate some of the superficial veins on your upper limbs and try to move them, you will find that the tunica externa prevents this. If the tunica externa did not hold the vessel in place, any movement would likely result in disruption of blood flow.

Arteries

An **artery** is a blood vessel that conducts blood away from the heart. All arteries have relatively thick walls that can withstand the high pressure of blood ejected from the heart. However, those close to the heart have the thickest walls, containing a high percentage of elastic fibers in all three of their tunics. This type of artery is known as an **elastic artery** ([link]). Vessels larger than 10 mm in diameter are typically elastic. Their abundant elastic fibers allow them to expand, as blood pumped from the ventricles passes through them, and then to recoil after the surge has passed. If artery walls were rigid and unable to expand and recoil, their resistance to blood

flow would greatly increase and blood pressure would rise to even higher levels, which would in turn require the heart to pump harder to increase the volume of blood expelled by each pump (the stroke volume) and maintain adequate pressure and flow. Artery walls would have to become even thicker in response to this increased pressure. The elastic recoil of the vascular wall helps to maintain the pressure gradient that drives the blood through the arterial system. An elastic artery is also known as a conducting artery, because the large diameter of the lumen enables it to accept a large volume of blood from the heart and conduct it to smaller branches.

Types of Arteries and Arterioles



Comparison of the walls of an elastic artery, a muscular artery, and an arteriole is shown. In terms of scale, the diameter of an arteriole is measured in micrometers compared to millimeters for elastic and muscular arteries.

Farther from the heart, where the surge of blood has dampened, the percentage of elastic fibers in an artery’s tunica intima decreases and the amount of smooth muscle in its tunica media increases. The artery at this point is described as a **muscular artery**. The diameter of muscular arteries typically ranges from 0.1 mm to 10 mm. Their thick tunica media allows muscular arteries to play a leading role in vasoconstriction. In contrast, their decreased quantity of elastic fibers limits their ability to expand. Fortunately, because the blood pressure has eased by the time it reaches these more distant vessels, elasticity has become less important.

Notice that although the distinctions between elastic and muscular arteries are important, there is no “line of demarcation” where an elastic artery suddenly becomes muscular. Rather, there is a gradual transition as the

vascular tree repeatedly branches. In turn, muscular arteries branch to distribute blood to the vast network of arterioles. For this reason, a muscular artery is also known as a distributing artery.

Arterioles

An **arteriole** is a very small artery that leads to a capillary. Arterioles have the same three tunics as the larger vessels, but the thickness of each is greatly diminished. The critical endothelial lining of the tunica intima is intact. The tunica media is restricted to one or two smooth muscle cell layers in thickness. The tunica externa remains but is very thin (see [link]).

With a lumen averaging 30 micrometers or less in diameter, arterioles are critical in slowing down—or resisting—blood flow and, thus, causing a substantial drop in blood pressure. Because of this, you may see them referred to as resistance vessels. The muscle fibers in arterioles are normally slightly contracted, causing arterioles to maintain a consistent muscle tone—in this case referred to as vascular tone—in a similar manner to the muscular tone of skeletal muscle. In reality, all blood vessels exhibit vascular tone due to the partial contraction of smooth muscle. The importance of the arterioles is that they will be the primary site of both resistance and regulation of blood pressure. The precise diameter of the lumen of an arteriole at any given moment is determined by neural and chemical controls, and vasoconstriction and vasodilation in the arterioles are the primary mechanisms for distribution of blood flow.

Capillaries

A **capillary** is a microscopic channel that supplies blood to the tissues themselves, a process called **perfusion**. Exchange of gases and other substances occurs in the capillaries between the blood and the surrounding cells and their tissue fluid (interstitial fluid). The diameter of a capillary lumen ranges from 5–10 micrometers; the smallest are just barely wide enough for an erythrocyte to squeeze through. Flow through capillaries is often described as **microcirculation**.

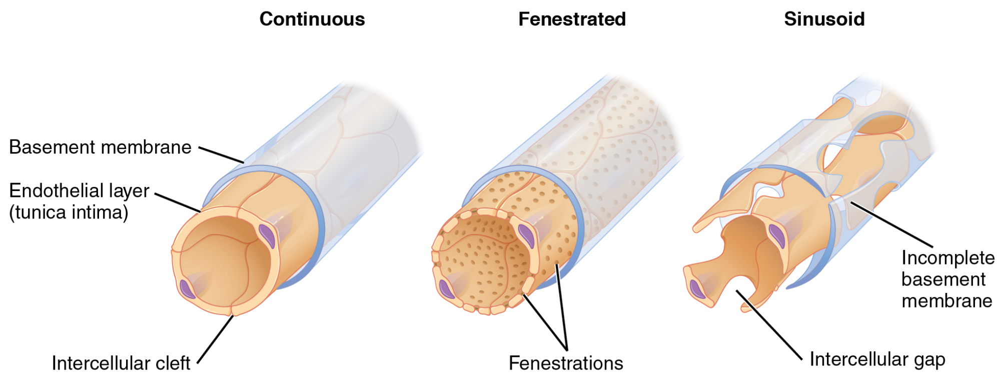
The wall of a capillary consists of the endothelial layer surrounded by a basement membrane with occasional smooth muscle fibers. There is some variation in wall structure: In a large capillary, several endothelial cells bordering each other may line the lumen; in a small capillary, there may be only a single cell layer that wraps around to contact itself.

For capillaries to function, their walls must be leaky, allowing substances to pass through. There are three major types of capillaries, which differ according to their degree of “leakiness:” continuous, fenestrated, and sinusoid capillaries ([link]).

Continuous Capillaries

The most common type of capillary, the **continuous capillary**, is found in almost all vascularized tissues. Continuous capillaries are characterized by a complete endothelial lining with tight junctions between endothelial cells. Although a tight junction is usually impermeable and only allows for the passage of water and ions, they are often incomplete in capillaries, leaving intercellular clefts that allow for exchange of water and other very small molecules between the blood plasma and the interstitial fluid. Substances that can pass between cells include metabolic products, such as glucose, water, and small hydrophobic molecules like gases and hormones, as well as various leukocytes. Continuous capillaries not associated with the brain are rich in transport vesicles, contributing to either endocytosis or exocytosis. Those in the brain are part of the blood-brain barrier. Here, there are tight junctions and no intercellular clefts, plus a thick basement membrane and astrocyte extensions called end feet; these structures combine to prevent the movement of nearly all substances.

Types of Capillaries



The three major types of capillaries: continuous, fenestrated, and sinusoid.

Fenestrated Capillaries

A **fenestrated capillary** is one that has pores (or fenestrations) in addition to tight junctions in the endothelial lining. These make the capillary permeable to larger molecules. The number of fenestrations and their degree of permeability vary, however, according to their location. Fenestrated capillaries are common in the small intestine, which is the primary site of nutrient absorption, as well as in the kidneys, which filter the blood. They are also found in the choroid plexus of the brain and many endocrine structures, including the hypothalamus, pituitary, pineal, and thyroid glands.

Sinusoid Capillaries

A **sinusoid capillary** (or sinusoid) is the least common type of capillary. Sinusoid capillaries are flattened, and they have extensive intercellular gaps and incomplete basement membranes, in addition to intercellular clefts and fenestrations. This gives them an appearance not unlike Swiss cheese. These very large openings allow for the passage of the largest molecules, including plasma proteins and even cells. Blood flow through sinusoids is

very slow, allowing more time for exchange of gases, nutrients, and wastes. Sinusoids are found in the liver and spleen, bone marrow, lymph nodes (where they carry lymph, not blood), and many endocrine glands including the pituitary and adrenal glands. Without these specialized capillaries, these organs would not be able to provide their myriad of functions. For example, when bone marrow forms new blood cells, the cells must enter the blood supply and can only do so through the large openings of a sinusoid capillary; they cannot pass through the small openings of continuous or fenestrated capillaries. The liver also requires extensive specialized sinusoid capillaries in order to process the materials brought to it by the hepatic portal vein from both the digestive tract and spleen, and to release plasma proteins into circulation.

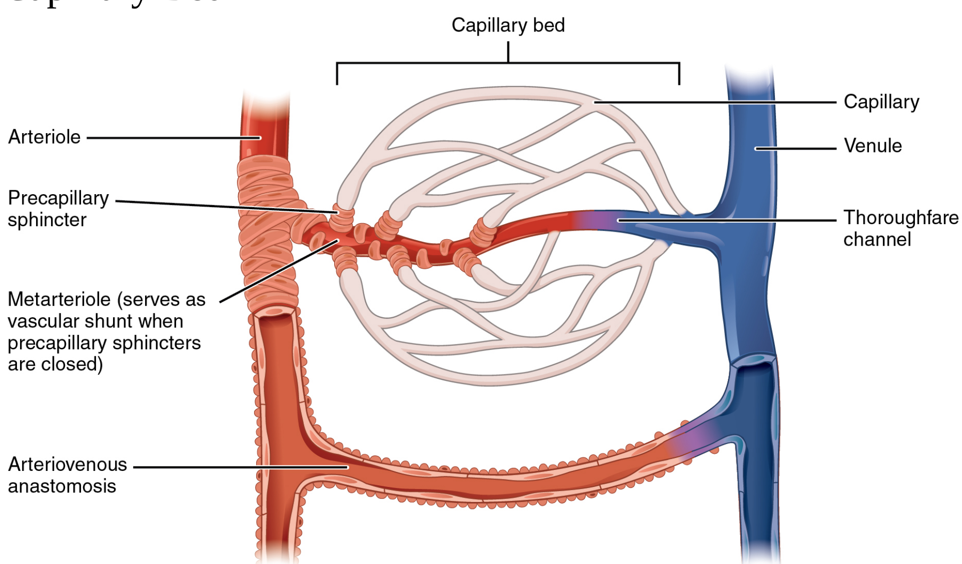
Metarterioles and Capillary Beds

A **metarteriole** is a type of vessel that has structural characteristics of both an arteriole and a capillary. Slightly larger than the typical capillary, the smooth muscle of the tunica media of the metarteriole is not continuous but forms rings of smooth muscle (sphincters) prior to the entrance to the capillaries. Each metarteriole arises from a terminal arteriole and branches to supply blood to a **capillary bed** that may consist of 10–100 capillaries.

The **precapillary sphincters**, circular smooth muscle cells that surround the capillary at its origin with the metarteriole, tightly regulate the flow of blood from a metarteriole to the capillaries it supplies. Their function is critical: If all of the capillary beds in the body were to open simultaneously, they would collectively hold every drop of blood in the body and there would be none in the arteries, arterioles, venules, veins, or the heart itself. Normally, the precapillary sphincters are closed. When the surrounding tissues need oxygen and have excess waste products, the precapillary sphincters open, allowing blood to flow through and exchange to occur before closing once more ([link]). If all of the precapillary sphincters in a capillary bed are closed, blood will flow from the metarteriole directly into a **thoroughfare channel** and then into the venous circulation, bypassing the capillary bed entirely. This creates what is known as a **vascular shunt**. In addition, an **arteriovenous anastomosis** may bypass the capillary bed and lead directly to the venous system.

Although you might expect blood flow through a capillary bed to be smooth, in reality, it moves with an irregular, pulsating flow. This pattern is called **vasomotion** and is regulated by chemical signals that are triggered in response to changes in internal conditions, such as oxygen, carbon dioxide, hydrogen ion, and lactic acid levels. For example, during strenuous exercise when oxygen levels decrease and carbon dioxide, hydrogen ion, and lactic acid levels all increase, the capillary beds in skeletal muscle are open, as they would be in the digestive system when nutrients are present in the digestive tract. During sleep or rest periods, vessels in both areas are largely closed; they open only occasionally to allow oxygen and nutrient supplies to travel to the tissues to maintain basic life processes.

Capillary Bed



In a capillary bed, arterioles give rise to metarterioles. Precapillary sphincters located at the junction of a metarteriole with a capillary regulate blood flow. A thoroughfare channel connects the metarteriole to a venule. An arteriovenous anastomosis, which directly connects the arteriole with the venule, is shown at the bottom.

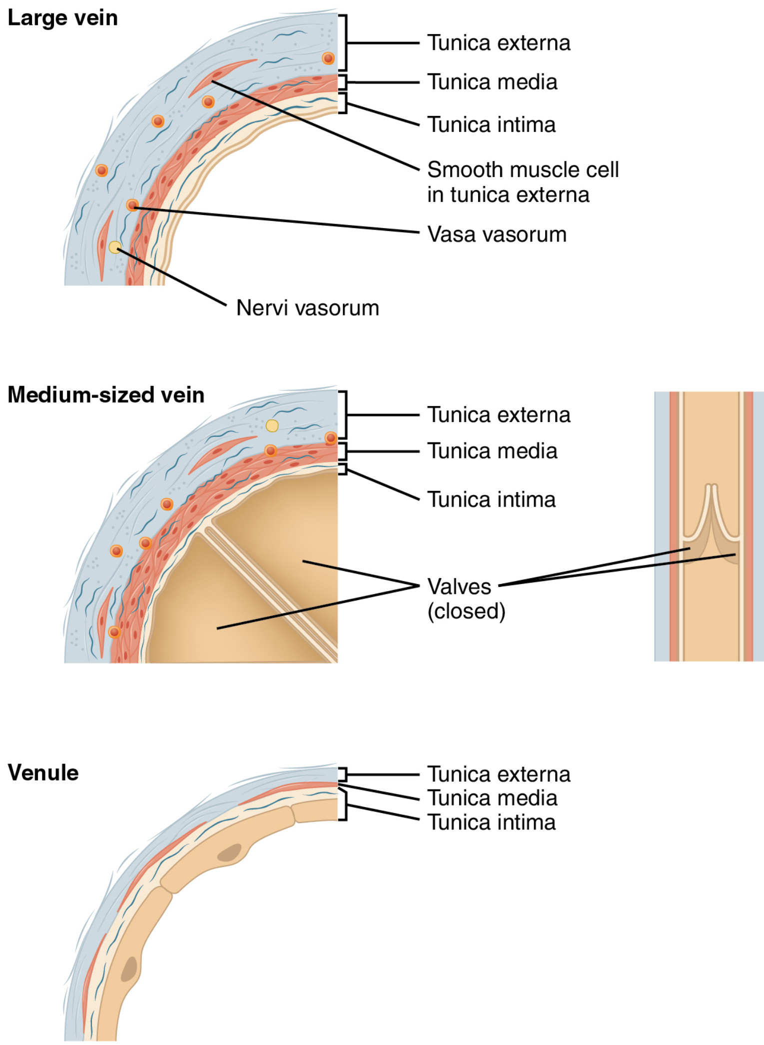
Venules

A **venule** is an extremely small vein, generally 8–100 micrometers in diameter. Postcapillary venules join multiple capillaries exiting from a capillary bed. Multiple venules join to form veins. The walls of venules consist of endothelium, a thin middle layer with a few muscle cells and elastic fibers, plus an outer layer of connective tissue fibers that constitute a very thin tunica externa ([link]). Venules as well as capillaries are the primary sites of emigration or diapedesis, in which the white blood cells adhere to the endothelial lining of the vessels and then squeeze through adjacent cells to enter the tissue fluid.

Veins

A **vein** is a blood vessel that conducts blood toward the heart. Compared to arteries, veins are thin-walled vessels with large and irregular lumens (see [link]). Because they are low-pressure vessels, larger veins are commonly equipped with valves that promote the unidirectional flow of blood toward the heart and prevent backflow toward the capillaries caused by the inherent low blood pressure in veins as well as the pull of gravity. [link] compares the features of arteries and veins.

Comparison of Veins and Venules



Many veins have valves to prevent back flow of blood, whereas venules do not. In terms of scale, the diameter of a venule is measured in micrometers compared to millimeters for veins.

Comparison of Arteries and Veins		
	Arteries	**Veins**
Direction of blood flow	Conducts blood away from the heart	Conducts blood toward the heart
General appearance	Rounded	Irregular, often collapsed
Pressure	High	Low
Wall thickness	Thick	Thin
Relative oxygen concentration	Higher in systemic arteries Lower in pulmonary arteries	Lower in systemic veins Higher in pulmonary veins
Valves	Not present	Present most commonly in limbs and in veins inferior to the heart

Note:
Disorders of the…
Cardiovascular System: Edema and Varicose Veins
Despite the presence of valves and the contributions of other anatomical and physiological adaptations we will cover shortly, over the course of a day, some blood will inevitably pool, especially in the lower limbs, due to the pull of gravity. Any blood that accumulates in a vein will increase the

pressure within it, which can then be reflected back into the smaller veins, venules, and eventually even the capillaries. Increased pressure will promote the flow of fluids out of the capillaries and into the interstitial fluid. The presence of excess tissue fluid around the cells leads to a condition called edema.

Most people experience a daily accumulation of tissue fluid, especially if they spend much of their work life on their feet (like most health professionals). However, clinical edema goes beyond normal swelling and requires medical treatment. Edema has many potential causes, including hypertension and heart failure, severe protein deficiency, renal failure, and many others. In order to treat edema, which is a sign rather than a discrete disorder, the underlying cause must be diagnosed and alleviated.

Varicose Veins

Varicose veins are commonly found in the lower limbs. (credit: Thomas Kriese)

Edema may be accompanied by varicose veins, especially in the superficial veins of the legs ([link]). This disorder arises when defective valves allow blood to accumulate within the veins, causing them to distend, twist, and become visible on the surface of the integument. Varicose veins may occur in both sexes, but are more common in women and are often related to pregnancy. More than simple cosmetic blemishes, varicose veins are often painful and sometimes itchy or throbbing. Without treatment, they tend to grow worse over time. The use of support hose, as well as elevating the feet and legs whenever possible, may be helpful in alleviating this condition. Laser surgery and interventional radiologic procedures can reduce the size and severity of varicose veins. Severe cases may require conventional surgery to remove the damaged vessels. As there are typically redundant circulation patterns, that is, anastomoses, for the smaller and more superficial veins, removal does not typically impair the circulation. There is evidence that patients with varicose veins suffer a greater risk of developing a thrombus or clot.

Veins as Blood Reservoirs

In addition to their primary function of returning blood to the heart, veins may be considered blood reservoirs, since systemic veins contain approximately 64 percent of the blood volume at any given time ([link]). Their ability to hold this much blood is due to their high **capacitance**, that is, their capacity to distend (expand) readily to store a high volume of blood, even at a low pressure. The large lumens and relatively thin walls of veins make them far more distensible than arteries; thus, they are said to be **capacitance vessels**.

Distribution of Blood Flow

Systemic circulation 84%	Systemic veins 64%	Large veins 18%
		Large venous networks (liver, bone marrow, and integument) 21%
		Venules and medium-sized veins 25%
	Systemic arteries 13%	Arterioles 2%
		Muscular arteries 5%
		Elastic arteries 4%
		Aorta 2%
	Systemic capillaries 7%	Systemic capillaries 7%
Pulmonary circulation 9%	Pulmonary veins 4%	
	Pulmonary capillaries 2%	
	Pulmonary arteries 3%	
Heart 7%		

When blood flow needs to be redistributed to other portions of the body, the vasomotor center located in the medulla oblongata sends sympathetic stimulation to the smooth muscles in the walls of the veins, causing constriction—or in this case, venoconstriction. Less dramatic than the vasoconstriction seen in smaller arteries and arterioles, venoconstriction may be likened to a “stiffening” of the vessel wall. This increases pressure on the blood within the veins, speeding its return to the heart. As you will note in [link], approximately 21 percent of the venous blood is located in venous networks within the liver, bone marrow, and integument. This volume of blood is referred to as **venous reserve**. Through venoconstriction, this “reserve” volume of blood can get back to the heart more quickly for redistribution to other parts of the circulation.

Note:
Career Connection
Vascular Surgeons and Technicians

Vascular surgery is a specialty in which the physician deals primarily with diseases of the vascular portion of the cardiovascular system. This includes repair and replacement of diseased or damaged vessels, removal of plaque from vessels, minimally invasive procedures including the insertion of venous catheters, and traditional surgery. Following completion of medical school, the physician generally completes a 5-year surgical residency followed by an additional 1 to 2 years of vascular specialty training. In the United States, most vascular surgeons are members of the Society of Vascular Surgery.

Vascular technicians are specialists in imaging technologies that provide information on the health of the vascular system. They may also assist physicians in treating disorders involving the arteries and veins. This profession often overlaps with cardiovascular technology, which would also include treatments involving the heart. Although recognized by the American Medical Association, there are currently no licensing requirements for vascular technicians, and licensing is voluntary. Vascular technicians typically have an Associate's degree or certificate, involving 18 months to 2 years of training. The United States Bureau of Labor projects this profession to grow by 29 percent from 2010 to 2020.

Note:

Visit this site to learn more about vascular surgery.

Note:

Visit this site to learn more about vascular technicians.

Chapter Review

Blood pumped by the heart flows through a series of vessels known as arteries, arterioles, capillaries, venules, and veins before returning to the heart. Arteries transport blood away from the heart and branch into smaller vessels, forming arterioles. Arterioles distribute blood to capillary beds, the sites of exchange with the body tissues. Capillaries lead back to small vessels known as venules that flow into the larger veins and eventually back to the heart.

The arterial system is a relatively high-pressure system, so arteries have thick walls that appear round in cross section. The venous system is a lower-pressure system, containing veins that have larger lumens and thinner walls. They often appear flattened. Arteries, arterioles, venules, and veins are composed of three tunics known as the tunica intima, tunica media, and tunica externa. Capillaries have only a tunica intima layer. The tunica intima is a thin layer composed of a simple squamous epithelium known as endothelium and a small amount of connective tissue. The tunica media is a thicker area composed of variable amounts of smooth muscle and connective tissue. It is the thickest layer in all but the largest arteries. The tunica externa is primarily a layer of connective tissue, although in veins, it also contains some smooth muscle. Blood flow through vessels can be dramatically influenced by vasoconstriction and vasodilation in their walls.

Review Questions

Exercise:

Problem: The endothelium is found in the ________.

a. tunica intima
b. tunica media
c. tunica externa
d. lumen

Solution:

A

Exercise:

Problem: Nervi vasorum control ________.

a. vasoconstriction
b. vasodilation
c. capillary permeability
d. both vasoconstriction and vasodilation

Solution:

D

Exercise:

Problem:

Closer to the heart, arteries would be expected to have a higher percentage of ________.

a. endothelium
b. smooth muscle fibers
c. elastic fibers
d. collagenous fibers

Solution:

C

Exercise:

Problem: Which of the following best describes veins?

a. thick walled, small lumens, low pressure, lack valves
b. thin walled, large lumens, low pressure, have valves
c. thin walled, small lumens, high pressure, have valves
d. thick walled, large lumens, high pressure, lack valves

Solution:

B

Exercise:

Problem:

An especially leaky type of capillary found in the liver and certain other tissues is called a _________.

a. capillary bed
b. fenestrated capillary
c. sinusoid capillary
d. metarteriole

Solution:

C

Critical Thinking Questions

Exercise:

Problem: Arterioles are often referred to as resistance vessels. Why?

Solution:

Arterioles receive blood from arteries, which are vessels with a much larger lumen. As their own lumen averages just 30 micrometers or less, arterioles are critical in slowing down—or resisting—blood flow. The arterioles can also constrict or dilate, which varies their resistance, to help distribute blood flow to the tissues.

Exercise:

Problem:

Cocaine use causes vasoconstriction. Is this likely to increase or decrease blood pressure, and why?

Solution:

Vasoconstriction causes the lumens of blood vessels to narrow. This increases the pressure of the blood flowing within the vessel.

Exercise:

Problem:

A blood vessel with a few smooth muscle fibers and connective tissue, and only a very thin tunica externa conducts blood toward the heart. What type of vessel is this?

Solution:

This is a venule.

Glossary

arteriole
: (also, resistance vessel) very small artery that leads to a capillary

arteriovenous anastomosis
: short vessel connecting an arteriole directly to a venule and bypassing the capillary beds

artery
: blood vessel that conducts blood away from the heart; may be a conducting or distributing vessel

capacitance
: ability of a vein to distend and store blood

capacitance vessels
: veins

capillary
: smallest of blood vessels where physical exchange occurs between the blood and tissue cells surrounded by interstitial fluid

capillary bed
: network of 10–100 capillaries connecting arterioles to venules

continuous capillary
: most common type of capillary, found in virtually all tissues except epithelia and cartilage; contains very small gaps in the endothelial lining that permit exchange

elastic artery
: (also, conducting artery) artery with abundant elastic fibers located closer to the heart, which maintains the pressure gradient and conducts blood to smaller branches

external elastic membrane
: membrane composed of elastic fibers that separates the tunica media from the tunica externa; seen in larger arteries

fenestrated capillary
: type of capillary with pores or fenestrations in the endothelium that allow for rapid passage of certain small materials

internal elastic membrane
membrane composed of elastic fibers that separates the tunica intima from the tunica media; seen in larger arteries

lumen
interior of a tubular structure such as a blood vessel or a portion of the alimentary canal through which blood, chyme, or other substances travel

metarteriole
short vessel arising from a terminal arteriole that branches to supply a capillary bed

microcirculation
blood flow through the capillaries

muscular artery
(also, distributing artery) artery with abundant smooth muscle in the tunica media that branches to distribute blood to the arteriole network

nervi vasorum
small nerve fibers found in arteries and veins that trigger contraction of the smooth muscle in their walls

perfusion
distribution of blood into the capillaries so the tissues can be supplied

precapillary sphincters
circular rings of smooth muscle that surround the entrance to a capillary and regulate blood flow into that capillary

sinusoid capillary
rarest type of capillary, which has extremely large intercellular gaps in the basement membrane in addition to clefts and fenestrations; found in areas such as the bone marrow and liver where passage of large molecules occurs

thoroughfare channel

continuation of the metarteriole that enables blood to bypass a capillary bed and flow directly into a venule, creating a vascular shunt

tunica externa
: (also, tunica adventitia) outermost layer or tunic of a vessel (except capillaries)

tunica intima
: (also, tunica interna) innermost lining or tunic of a vessel

tunica media
: middle layer or tunic of a vessel (except capillaries)

vasa vasorum
: small blood vessels located within the walls or tunics of larger vessels that supply nourishment to and remove wastes from the cells of the vessels

vascular shunt
: continuation of the metarteriole and thoroughfare channel that allows blood to bypass the capillary beds to flow directly from the arterial to the venous circulation

vasoconstriction
: constriction of the smooth muscle of a blood vessel, resulting in a decreased vascular diameter

vasodilation
: relaxation of the smooth muscle in the wall of a blood vessel, resulting in an increased vascular diameter

vasomotion
: irregular, pulsating flow of blood through capillaries and related structures

vein
: blood vessel that conducts blood toward the heart

venous reserve

volume of blood contained within systemic veins in the integument, bone marrow, and liver that can be returned to the heart for circulation, if needed

venule

small vessel leading from the capillaries to veins

Homeostatic Regulation of the Vascular System
By the end of this section, you will be able to:

- Discuss the mechanisms involved in the neural regulation of vascular homeostasis
- Describe the contribution of a variety of hormones to the renal regulation of blood pressure
- Identify the effects of exercise on vascular homeostasis
- Discuss how hypertension, hemorrhage, and circulatory shock affect vascular health

In order to maintain homeostasis in the cardiovascular system and provide adequate blood to the tissues, blood flow must be redirected continually to the tissues as they become more active. In a very real sense, the cardiovascular system engages in resource allocation, because there is not enough blood flow to distribute blood equally to all tissues simultaneously. For example, when an individual is exercising, more blood will be directed to skeletal muscles, the heart, and the lungs. Following a meal, more blood is directed to the digestive system. Only the brain receives a more or less constant supply of blood whether you are active, resting, thinking, or engaged in any other activity.

[link] provides the distribution of systemic blood at rest and during exercise. Although most of the data appears logical, the values for the distribution of blood to the integument may seem surprising. During exercise, the body distributes more blood to the body surface where it can dissipate the excess heat generated by increased activity into the environment.

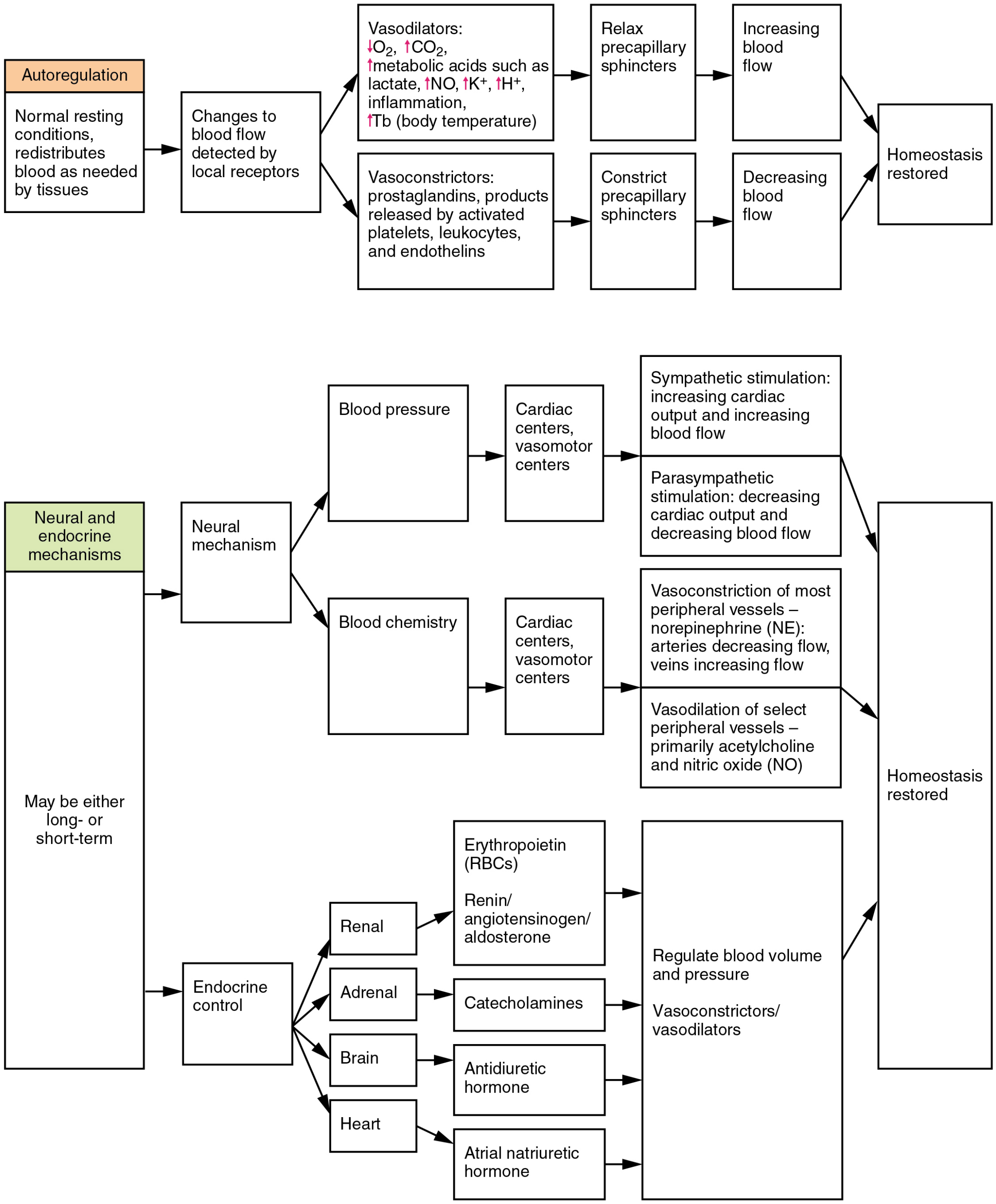
Systemic Blood Flow During Rest, Mild Exercise, and Maximal Exercise in a Healthy Young Individual

Systemic Blood Flow During Rest, Mild Exercise, and Maximal Exercise in a Healthy Young Individual

Organ	Resting (mL/min)	Mild exercise (mL/min)	Maximal exercise (mL/min)
Skeletal muscle	1200	4500	12,500
Heart	250	350	750
Brain	750	750	750
Integument	500	1500	1900
Kidney	1100	900	600
Gastrointestinal	1400	1100	600
Others (i.e., liver, spleen)	600	400	400
Total	5800	9500	17,500

Three homeostatic mechanisms ensure adequate blood flow, blood pressure, distribution, and ultimately perfusion: neural, endocrine, and autoregulatory mechanisms. They are summarized in [link].

Summary of Factors Maintaining Vascular Homeostasis



Adequate blood flow, blood pressure, distribution, and perfusion involve autoregulatory, neural, and endocrine mechanisms.

Neural Regulation

The nervous system plays a critical role in the regulation of vascular homeostasis. The primary regulatory sites include the cardiovascular centers in the brain that control both cardiac and vascular functions. In addition, more generalized neural responses from the limbic system and the autonomic nervous system are factors.

The Cardiovascular Centers in the Brain

Neurological regulation of blood pressure and flow depends on the cardiovascular centers located in the medulla oblongata. This cluster of neurons responds to changes in blood pressure as well as blood concentrations of oxygen, carbon dioxide, and hydrogen ions. The cardiovascular center contains three distinct paired components:

- The cardioaccelerator centers stimulate cardiac function by regulating heart rate and stroke volume via sympathetic stimulation from the cardiac accelerator nerve.
- The cardioinhibitor centers slow cardiac function by decreasing heart rate and stroke volume via parasympathetic stimulation from the vagus nerve.
- The vasomotor centers control vessel tone or contraction of the smooth muscle in the tunica media. Changes in diameter affect peripheral resistance, pressure, and flow, which affect cardiac output. The majority of these neurons act via the release of the neurotransmitter norepinephrine from sympathetic neurons.

Although each center functions independently, they are not anatomically distinct.

There is also a small population of neurons that control vasodilation in the vessels of the brain and skeletal muscles by relaxing the smooth muscle fibers in the vessel tunics. Many of these are cholinergic neurons, that is, they release acetylcholine, which in turn stimulates the vessels’ endothelial cells to release nitric oxide (NO), which causes vasodilation. Others release

norepinephrine that binds to β_2 receptors. A few neurons release NO directly as a neurotransmitter.

Recall that mild stimulation of the skeletal muscles maintains muscle tone. A similar phenomenon occurs with vascular tone in vessels. As noted earlier, arterioles are normally partially constricted: With maximal stimulation, their radius may be reduced to one-half of the resting state. Full dilation of most arterioles requires that this sympathetic stimulation be suppressed. When it is, an arteriole can expand by as much as 150 percent. Such a significant increase can dramatically affect resistance, pressure, and flow.

Baroreceptor Reflexes

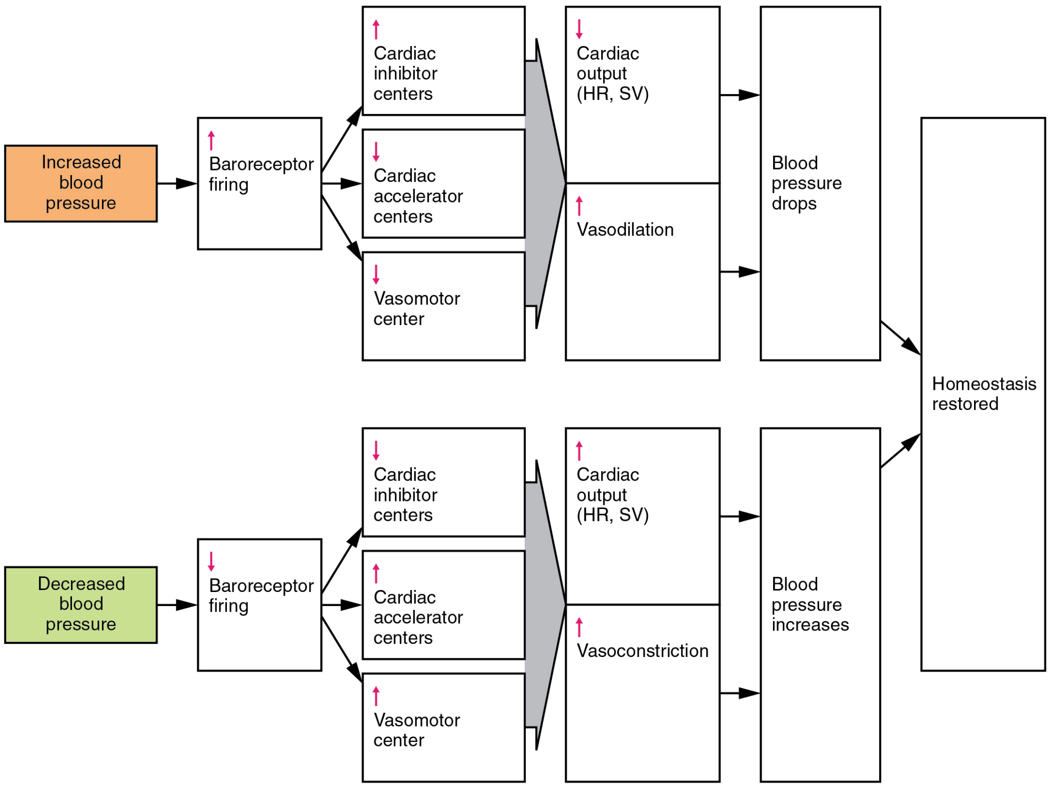
Baroreceptors are specialized stretch receptors located within thin areas of blood vessels and heart chambers that respond to the degree of stretch caused by the presence of blood. They send impulses to the cardiovascular center to regulate blood pressure. Vascular baroreceptors are found primarily in sinuses (small cavities) within the aorta and carotid arteries: The **aortic sinuses** are found in the walls of the ascending aorta just superior to the aortic valve, whereas the **carotid sinuses** are in the base of the internal carotid arteries. There are also low-pressure baroreceptors located in the walls of the venae cavae and right atrium.

When blood pressure increases, the baroreceptors are stretched more tightly and initiate action potentials at a higher rate. At lower blood pressures, the degree of stretch is lower and the rate of firing is slower. When the cardiovascular center in the medulla oblongata receives this input, it triggers a reflex that maintains homeostasis ([link]):

- When blood pressure rises too high, the baroreceptors fire at a higher rate and trigger parasympathetic stimulation of the heart. As a result, cardiac output falls. Sympathetic stimulation of the peripheral arterioles will also decrease, resulting in vasodilation. Combined, these activities cause blood pressure to fall.

- When blood pressure drops too low, the rate of baroreceptor firing decreases. This will trigger an increase in sympathetic stimulation of the heart, causing cardiac output to increase. It will also trigger sympathetic stimulation of the peripheral vessels, resulting in vasoconstriction. Combined, these activities cause blood pressure to rise.

Baroreceptor Reflexes for Maintaining Vascular Homeostasis



Increased blood pressure results in increased rates of baroreceptor firing, whereas decreased blood pressure results in slower rates of fire, both initiating the homeostatic mechanism to restore blood pressure.

The baroreceptors in the venae cavae and right atrium monitor blood pressure as the blood returns to the heart from the systemic circulation. Normally, blood flow into the aorta is the same as blood flow back into the right atrium. If blood is returning to the right atrium more rapidly than it is

being ejected from the left ventricle, the atrial receptors will stimulate the cardiovascular centers to increase sympathetic firing and increase cardiac output until homeostasis is achieved. The opposite is also true. This mechanism is referred to as the **atrial reflex**.

Chemoreceptor Reflexes

In addition to the baroreceptors are chemoreceptors that monitor levels of oxygen, carbon dioxide, and hydrogen ions (pH), and thereby contribute to vascular homeostasis. Chemoreceptors monitoring the blood are located in close proximity to the baroreceptors in the aortic and carotid sinuses. They signal the cardiovascular center as well as the respiratory centers in the medulla oblongata.

Since tissues consume oxygen and produce carbon dioxide and acids as waste products, when the body is more active, oxygen levels fall and carbon dioxide levels rise as cells undergo cellular respiration to meet the energy needs of activities. This causes more hydrogen ions to be produced, causing the blood pH to drop. When the body is resting, oxygen levels are higher, carbon dioxide levels are lower, more hydrogen is bound, and pH rises. (Seek additional content for more detail about pH.)

The chemoreceptors respond to increasing carbon dioxide and hydrogen ion levels (falling pH) by stimulating the cardioaccelerator and vasomotor centers, increasing cardiac output and constricting peripheral vessels. The cardioinhibitor centers are suppressed. With falling carbon dioxide and hydrogen ion levels (increasing pH), the cardioinhibitor centers are stimulated, and the cardioaccelerator and vasomotor centers are suppressed, decreasing cardiac output and causing peripheral vasodilation. In order to maintain adequate supplies of oxygen to the cells and remove waste products such as carbon dioxide, it is essential that the respiratory system respond to changing metabolic demands. In turn, the cardiovascular system will transport these gases to the lungs for exchange, again in accordance with metabolic demands. This interrelationship of cardiovascular and respiratory control cannot be overemphasized.

Other neural mechanisms can also have a significant impact on cardiovascular function. These include the limbic system that links physiological responses to psychological stimuli, as well as generalized sympathetic and parasympathetic stimulation.

Endocrine Regulation

Endocrine control over the cardiovascular system involves the catecholamines, epinephrine and norepinephrine, as well as several hormones that interact with the kidneys in the regulation of blood volume.

Epinephrine and Norepinephrine

The catecholamines epinephrine and norepinephrine are released by the adrenal medulla, and enhance and extend the body's sympathetic or "fight-or-flight" response (see [link]). They increase heart rate and force of contraction, while temporarily constricting blood vessels to organs not essential for flight-or-fight responses and redirecting blood flow to the liver, muscles, and heart.

Antidiuretic Hormone

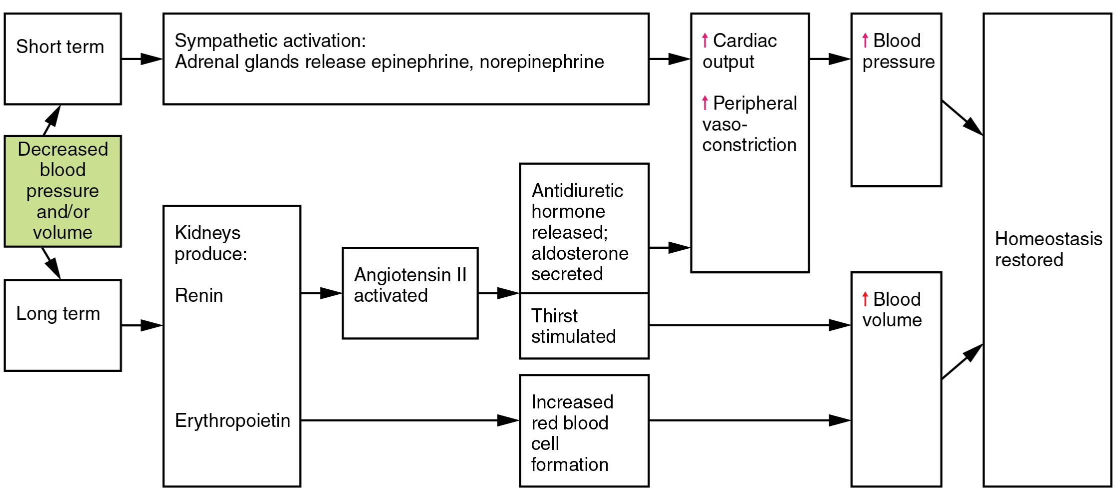
Antidiuretic hormone (ADH), also known as vasopressin, is secreted by the cells in the hypothalamus and transported via the hypothalamic-hypophyseal tracts to the posterior pituitary where it is stored until released upon nervous stimulation. The primary trigger prompting the hypothalamus to release ADH is increasing osmolarity of tissue fluid, usually in response to significant loss of blood volume. ADH signals its target cells in the kidneys to reabsorb more water, thus preventing the loss of additional fluid in the urine. This will increase overall fluid levels and help restore blood volume and pressure. In addition, ADH constricts peripheral vessels.

Renin-Angiotensin-Aldosterone Mechanism

The renin-angiotensin-aldosterone mechanism has a major effect upon the cardiovascular system ([link]). Renin is an enzyme, although because of its importance in the renin-angiotensin-aldosterone pathway, some sources identify it as a hormone. Specialized cells in the kidneys found in the juxtaglomerular apparatus respond to decreased blood flow by secreting renin into the blood. Renin converts the plasma protein angiotensinogen, which is produced by the liver, into its active form—angiotensin I. Angiotensin I circulates in the blood and is then converted into angiotensin II in the lungs. This reaction is catalyzed by the enzyme angiotensin-converting enzyme (ACE).

Angiotensin II is a powerful vasoconstrictor, greatly increasing blood pressure. It also stimulates the release of ADH and aldosterone, a hormone produced by the adrenal cortex. Aldosterone increases the reabsorption of sodium into the blood by the kidneys. Since water follows sodium, this increases the reabsorption of water. This in turn increases blood volume, raising blood pressure. Angiotensin II also stimulates the thirst center in the hypothalamus, so an individual will likely consume more fluids, again increasing blood volume and pressure.

Hormones Involved in Renal Control of Blood Pressure



In the renin-angiotensin-aldosterone mechanism, increasing angiotensin II will stimulate the production of antidiuretic hormone and aldosterone. In addition to renin, the kidneys

produce erythropoietin, which stimulates the production of red blood cells, further increasing blood volume.

Erythropoietin

Erythropoietin (EPO) is released by the kidneys when blood flow and/or oxygen levels decrease. EPO stimulates the production of erythrocytes within the bone marrow. Erythrocytes are the major formed element of the blood and may contribute 40 percent or more to blood volume, a significant factor of viscosity, resistance, pressure, and flow. In addition, EPO is a vasoconstrictor. Overproduction of EPO or excessive intake of synthetic EPO, often to enhance athletic performance, will increase viscosity, resistance, and pressure, and decrease flow in addition to its contribution as a vasoconstrictor.

Atrial Natriuretic Hormone

Secreted by cells in the atria of the heart, atrial natriuretic hormone (ANH) (also known as atrial natriuretic peptide) is secreted when blood volume is high enough to cause extreme stretching of the cardiac cells. Cells in the ventricle produce a hormone with similar effects, called B-type natriuretic hormone. Natriuretic hormones are antagonists to angiotensin II. They promote loss of sodium and water from the kidneys, and suppress renin, aldosterone, and ADH production and release. All of these actions promote loss of fluid from the body, so blood volume and blood pressure drop.

Autoregulation of Perfusion

As the name would suggest, autoregulation mechanisms require neither specialized nervous stimulation nor endocrine control. Rather, these are local, self-regulatory mechanisms that allow each region of tissue to adjust

its blood flow—and thus its perfusion. These local mechanisms include chemical signals and myogenic controls.

Chemical Signals Involved in Autoregulation

Chemical signals work at the level of the precapillary sphincters to trigger either constriction or relaxation. As you know, opening a precapillary sphincter allows blood to flow into that particular capillary, whereas constricting a precapillary sphincter temporarily shuts off blood flow to that region. The factors involved in regulating the precapillary sphincters include the following:

- Opening of the sphincter is triggered in response to decreased oxygen concentrations; increased carbon dioxide concentrations; increasing levels of lactic acid or other byproducts of cellular metabolism; increasing concentrations of potassium ions or hydrogen ions (falling pH); inflammatory chemicals such as histamines; and increased body temperature. These conditions in turn stimulate the release of NO, a powerful vasodilator, from endothelial cells (see [link]).
- Contraction of the precapillary sphincter is triggered by the opposite levels of the regulators, which prompt the release of endothelins, powerful vasoconstricting peptides secreted by endothelial cells. Platelet secretions and certain prostaglandins may also trigger constriction.

Again, these factors alter tissue perfusion via their effects on the precapillary sphincter mechanism, which regulates blood flow to capillaries. Since the amount of blood is limited, not all capillaries can fill at once, so blood flow is allocated based upon the needs and metabolic state of the tissues as reflected in these parameters. Bear in mind, however, that dilation and constriction of the arterioles feeding the capillary beds is the primary control mechanism.

The Myogenic Response

The **myogenic response** is a reaction to the stretching of the smooth muscle in the walls of arterioles as changes in blood flow occur through the vessel. This may be viewed as a largely protective function against dramatic fluctuations in blood pressure and blood flow to maintain homeostasis. If perfusion of an organ is too low (ischemia), the tissue will experience low levels of oxygen (hypoxia). In contrast, excessive perfusion could damage the organ's smaller and more fragile vessels. The myogenic response is a localized process that serves to stabilize blood flow in the capillary network that follows that arteriole.

When blood flow is low, the vessel's smooth muscle will be only minimally stretched. In response, it relaxes, allowing the vessel to dilate and thereby increase the movement of blood into the tissue. When blood flow is too high, the smooth muscle will contract in response to the increased stretch, prompting vasoconstriction that reduces blood flow.

[link] summarizes the effects of nervous, endocrine, and local controls on arterioles.

Summary of Mechanisms Regulating Arteriole Smooth Muscle and Veins

Control	Factor	Vasoconstriction	Vasodilation
Neural	Sympathetic stimulation	Arterioles within integument, abdominal viscera, and mucosa membrane; skeletal muscle (at high levels); varied in veins and venules	Arterioles within heart; skeletal muscles at low to moderate levels
	Parasympathetic	No known innervation for most	Arterioles in external genitalia, no known innervation for most other arterioles or veins
Endocrine	Epinephrine	Similar to sympathetic stimulation for extended flight-or-fight responses; at high levels, binds to specialized alpha (α) receptors	Similar to sympathetic stimulation for extended fight-or-flight responses; at low to moderate levels, binds to specialized beta (β) receptors
	Norepinephrine	Similar to epinephrine	Similar to epinephrine
	Angiotensin II	Powerful generalized vasoconstrictor; also stimulates release of aldosterone and ADH	n/a
	ANH (peptide)	n/a	Powerful generalized vasodilator; also promotes loss of fluid volume from kidneys, hence reducing blood volume, pressure, and flow
	ADH	Moderately strong generalized vasoconstrictor; also causes body to retain more fluid via kidneys, increasing blood volume and pressure	n/a
Other factors	Decreasing levels of oxygen	n/a	Vasodilation, also opens precapillary sphincters
	Decreasing pH	n/a	Vasodilation, also opens precapillary sphincters
	Increasing levels of carbon dioxide	n/a	Vasodilation, also opens precapillary sphincters
	Increasing levels of potassium ion	n/a	Vasodilation, also opens precapillary sphincters
	Increasing levels of prostaglandins	Vasoconstriction, closes precapillary sphincters for many	Vasodilation, opens precapillary sphincters for many
	Increasing levels of adenosine	n/a	Vasodilation
	Increasing levels of NO	n/a	Vasodilation, also opens precapillary sphincters
	Increasing levels of lactic acid and other metabolites	n/a	Vasodilation, also opens precapillary sphincters
	Increasing levels of endothelins	Vasoconstriction	n/a
	Increasing levels of platelet secretions	Vasoconstriction	n/a
	Increasing hyperthermia	n/a	Vasodilation
	Stretching of vascular wall (myogenic)	Vasoconstriction	n/a
	Increasing levels of histamines from basophils and mast cells	n/a	Vasodilation

Effect of Exercise on Vascular Homeostasis

The heart is a muscle and, like any muscle, it responds dramatically to exercise. For a healthy young adult, cardiac output (heart rate × stroke volume) increases in the nonathlete from approximately 5.0 liters (5.25 quarts) per minute to a maximum of about 20 liters (21 quarts) per minute. Accompanying this will be an increase in blood pressure from about 120/80 to 185/75. However, well-trained aerobic athletes can increase these values

substantially. For these individuals, cardiac output soars from approximately 5.3 liters (5.57 quarts) per minute resting to more than 30 liters (31.5 quarts) per minute during maximal exercise. Along with this increase in cardiac output, blood pressure increases from 120/80 at rest to 200/90 at maximum values.

In addition to improved cardiac function, exercise increases the size and mass of the heart. The average weight of the heart for the nonathlete is about 300 g, whereas in an athlete it will increase to 500 g. This increase in size generally makes the heart stronger and more efficient at pumping blood, increasing both stroke volume and cardiac output.

Tissue perfusion also increases as the body transitions from a resting state to light exercise and eventually to heavy exercise (see [link]). These changes result in selective vasodilation in the skeletal muscles, heart, lungs, liver, and integument. Simultaneously, vasoconstriction occurs in the vessels leading to the kidneys and most of the digestive and reproductive organs. The flow of blood to the brain remains largely unchanged whether at rest or exercising, since the vessels in the brain largely do not respond to regulatory stimuli, in most cases, because they lack the appropriate receptors.

As vasodilation occurs in selected vessels, resistance drops and more blood rushes into the organs they supply. This blood eventually returns to the venous system. Venous return is further enhanced by both the skeletal muscle and respiratory pumps. As blood returns to the heart more quickly, preload rises and the Frank-Starling principle tells us that contraction of the cardiac muscle in the atria and ventricles will be more forceful. Eventually, even the best-trained athletes will fatigue and must undergo a period of rest following exercise. Cardiac output and distribution of blood then return to normal.

Regular exercise promotes cardiovascular health in a variety of ways. Because an athlete’s heart is larger than a nonathlete’s, stroke volume increases, so the athletic heart can deliver the same amount of blood as the nonathletic heart but with a lower heart rate. This increased efficiency allows the athlete to exercise for longer periods of time before muscles fatigue and places less stress on the heart. Exercise also lowers overall

cholesterol levels by removing from the circulation a complex form of cholesterol, triglycerides, and proteins known as low-density lipoproteins (LDLs), which are widely associated with increased risk of cardiovascular disease. Although there is no way to remove deposits of plaque from the walls of arteries other than specialized surgery, exercise does promote the health of vessels by decreasing the rate of plaque formation and reducing blood pressure, so the heart does not have to generate as much force to overcome resistance.

Generally as little as 30 minutes of noncontinuous exercise over the course of each day has beneficial effects and has been shown to lower the rate of heart attack by nearly 50 percent. While it is always advisable to follow a healthy diet, stop smoking, and lose weight, studies have clearly shown that fit, overweight people may actually be healthier overall than sedentary slender people. Thus, the benefits of moderate exercise are undeniable.

Clinical Considerations in Vascular Homeostasis

Any disorder that affects blood volume, vascular tone, or any other aspect of vascular functioning is likely to affect vascular homeostasis as well. That includes hypertension, hemorrhage, and shock.

Hypertension and Hypotension

Chronically elevated blood pressure is known clinically as **hypertension**. It is defined as chronic and persistent blood pressure measurements of 140/90 mm Hg or above. Pressures between 120/80 and 140/90 mm Hg are defined as prehypertension. About 68 million Americans currently suffer from hypertension. Unfortunately, hypertension is typically a silent disorder; therefore, hypertensive patients may fail to recognize the seriousness of their condition and fail to follow their treatment plan. The result is often a heart attack or stroke. Hypertension may also lead to an aneurism (ballooning of a blood vessel caused by a weakening of the wall), peripheral arterial disease (obstruction of vessels in peripheral regions of the body), chronic kidney disease, or heart failure.

Note:

Listen to this CDC podcast to learn about hypertension, often described as a “silent killer.” What steps can you take to reduce your risk of a heart attack or stroke?

Hemorrhage

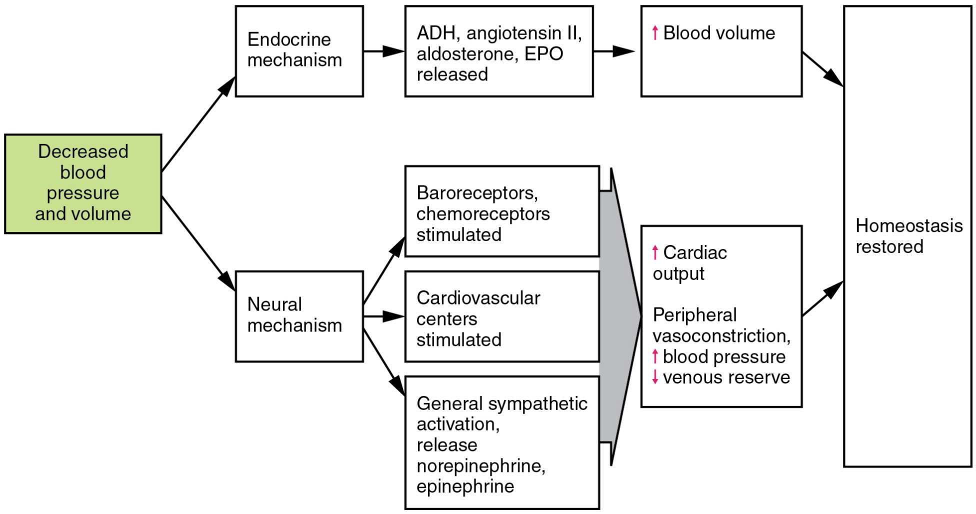
Minor blood loss is managed by hemostasis and repair. Hemorrhage is a loss of blood that cannot be controlled by hemostatic mechanisms. Initially, the body responds to hemorrhage by initiating mechanisms aimed at increasing blood pressure and maintaining blood flow. Ultimately, however, blood volume will need to be restored, either through physiological processes or through medical intervention.

In response to blood loss, stimuli from the baroreceptors trigger the cardiovascular centers to stimulate sympathetic responses to increase cardiac output and vasoconstriction. This typically prompts the heart rate to increase to about 180–200 contractions per minute, restoring cardiac output to normal levels. Vasoconstriction of the arterioles increases vascular resistance, whereas constriction of the veins increases venous return to the heart. Both of these steps will help increase blood pressure. Sympathetic stimulation also triggers the release of epinephrine and norepinephrine, which enhance both cardiac output and vasoconstriction. If blood loss were less than 20 percent of total blood volume, these responses together would usually return blood pressure to normal and redirect the remaining blood to the tissues.

Additional endocrine involvement is necessary, however, to restore the lost blood volume. The angiotensin-renin-aldosterone mechanism stimulates the

thirst center in the hypothalamus, which increases fluid consumption to help restore the lost blood. More importantly, it increases renal reabsorption of sodium and water, reducing water loss in urine output. The kidneys also increase the production of EPO, stimulating the formation of erythrocytes that not only deliver oxygen to the tissues but also increase overall blood volume. [link] summarizes the responses to loss of blood volume.

Homeostatic Responses to Loss of Blood Volume



Circulatory Shock

The loss of too much blood may lead to **circulatory shock**, a life-threatening condition in which the circulatory system is unable to maintain blood flow to adequately supply sufficient oxygen and other nutrients to the tissues to maintain cellular metabolism. It should not be confused with emotional or psychological shock. Typically, the patient in circulatory shock will demonstrate an increased heart rate but decreased blood pressure, but there are cases in which blood pressure will remain normal. Urine output will fall dramatically, and the patient may appear confused or lose consciousness. Urine output less than 1 mL/kg body weight/hour is cause for concern. Unfortunately, shock is an example of a positive-feedback loop that, if uncorrected, may lead to the death of the patient.

There are several recognized forms of shock:

- **Hypovolemic shock** in adults is typically caused by hemorrhage, although in children it may be caused by fluid losses related to severe vomiting or diarrhea. Other causes for hypovolemic shock include extensive burns, exposure to some toxins, and excessive urine loss related to diabetes insipidus or ketoacidosis. Typically, patients present with a rapid, almost tachycardic heart rate; a weak pulse often described as “thread;” cool, clammy skin, particularly in the extremities, due to restricted peripheral blood flow; rapid, shallow breathing; hypothermia; thirst; and dry mouth. Treatments generally involve providing intravenous fluids to restore the patient to normal function and various drugs such as dopamine, epinephrine, and norepinephrine to raise blood pressure.
- **Cardiogenic shock** results from the inability of the heart to maintain cardiac output. Most often, it results from a myocardial infarction (heart attack), but it may also be caused by arrhythmias, valve disorders, cardiomyopathies, cardiac failure, or simply insufficient flow of blood through the cardiac vessels. Treatment involves repairing the damage to the heart or its vessels to resolve the underlying cause, rather than treating cardiogenic shock directly.
- **Vascular shock** occurs when arterioles lose their normal muscular tone and dilate dramatically. It may arise from a variety of causes, and treatments almost always involve fluid replacement and medications, called inotropic or pressor agents, which restore tone to the muscles of the vessels. In addition, eliminating or at least alleviating the underlying cause of the condition is required. This might include antibiotics and antihistamines, or select steroids, which may aid in the repair of nerve damage. A common cause is **sepsis** (or septicemia), also called “blood poisoning,” which is a widespread bacterial infection that results in an organismal-level inflammatory response known as **septic shock**. **Neurogenic shock** is a form of vascular shock that occurs with cranial or spinal injuries that damage the cardiovascular centers in the medulla oblongata or the nervous fibers originating from this region. **Anaphylactic shock** is a severe allergic response that causes the widespread release of histamines, triggering vasodilation throughout the body.
- **Obstructive shock**, as the name would suggest, occurs when a significant portion of the vascular system is blocked. It is not always

recognized as a distinct condition and may be grouped with cardiogenic shock, including pulmonary embolism and cardiac tamponade. Treatments depend upon the underlying cause and, in addition to administering fluids intravenously, often include the administration of anticoagulants, removal of fluid from the pericardial cavity, or air from the thoracic cavity, and surgery as required. The most common cause is a pulmonary embolism, a clot that lodges in the pulmonary vessels and interrupts blood flow. Other causes include stenosis of the aortic valve; cardiac tamponade, in which excess fluid in the pericardial cavity interferes with the ability of the heart to fully relax and fill with blood (resulting in decreased preload); and a pneumothorax, in which an excessive amount of air is present in the thoracic cavity, outside of the lungs, which interferes with venous return, pulmonary function, and delivery of oxygen to the tissues.

Chapter Review

Neural, endocrine, and autoregulatory mechanisms affect blood flow, blood pressure, and eventually perfusion of blood to body tissues. Neural mechanisms include the cardiovascular centers in the medulla oblongata, baroreceptors in the aorta and carotid arteries and right atrium, and associated chemoreceptors that monitor blood levels of oxygen, carbon dioxide, and hydrogen ions. Endocrine controls include epinephrine and norepinephrine, as well as ADH, the renin-angiotensin-aldosterone mechanism, ANH, and EPO. Autoregulation is the local control of vasodilation and constriction by chemical signals and the myogenic response. Exercise greatly improves cardiovascular function and reduces the risk of cardiovascular diseases, including hypertension, a leading cause of heart attacks and strokes. Significant hemorrhage can lead to a form of circulatory shock known as hypovolemic shock. Sepsis, obstruction, and widespread inflammation can also cause circulatory shock.

Interactive Link Questions

Exercise:

Problem:

Listen to this CDC podcast to learn about hypertension, often described as a “silent killer.” What steps can you take to reduce your risk of a heart attack or stroke?

Solution:

Take medications as prescribed, eat a healthy diet, exercise, and don’t smoke.

Review Questions

Exercise:

Problem:

Clusters of neurons in the medulla oblongata that regulate blood pressure are known collectively as ________.

a. baroreceptors
b. angioreceptors
c. the cardiomotor mechanism
d. the cardiovascular center

Solution:

D

Exercise:

Problem: In the renin-angiotensin-aldosterone mechanism, ________.

a. decreased blood pressure prompts the release of renin from the liver
b. aldosterone prompts increased urine output
c. aldosterone prompts the kidneys to reabsorb sodium

d. all of the above

Solution:

C

Exercise:

Problem: In the myogenic response, _________.

a. muscle contraction promotes venous return to the heart
b. ventricular contraction strength is decreased
c. vascular smooth muscle responds to stretch
d. endothelins dilate muscular arteries

Solution:

C

Exercise:

Problem:

A form of circulatory shock common in young children with severe diarrhea or vomiting is _________.

a. hypovolemic shock
b. anaphylactic shock
c. obstructive shock
d. hemorrhagic shock

Solution:

A

Critical Thinking Questions

Exercise:

Problem:

A patient arrives in the emergency department with a blood pressure of 70/45 confused and complaining of thirst. Why?

Solution:

This blood pressure is insufficient to circulate blood throughout the patient's body and maintain adequate perfusion of the patient's tissues. Ischemia would prompt hypoxia, including to the brain, prompting confusion. The low blood pressure would also trigger the renin-angiotensin-aldosterone mechanism, and release of aldosterone would stimulate the thirst mechanism in the hypothalamus.

Exercise:

Problem:

Nitric oxide is broken down very quickly after its release. Why?

Solution:

Nitric oxide is a very powerful local vasodilator that is important in the autoregulation of tissue perfusion. If it were not broken down very quickly after its release, blood flow to the region could exceed metabolic needs.

References

Centers for Disease Control and Prevention (US). Getting blood pressure under control: high blood pressure is out of control for too many Americans [Internet]. Atlanta (GA); [cited 2013 Apr 26]. Available from: http://www.cdc.gov/features/vitalsigns/hypertension/

Glossary

anaphylactic shock
: type of shock that follows a severe allergic reaction and results from massive vasodilation

aortic sinuses
: small pockets in the ascending aorta near the aortic valve that are the locations of the baroreceptors (stretch receptors) and chemoreceptors that trigger a reflex that aids in the regulation of vascular homeostasis

atrial reflex
: mechanism for maintaining vascular homeostasis involving atrial baroreceptors: if blood is returning to the right atrium more rapidly than it is being ejected from the left ventricle, the atrial receptors will stimulate the cardiovascular centers to increase sympathetic firing and increase cardiac output until the situation is reversed; the opposite is also true

cardiogenic shock
: type of shock that results from the inability of the heart to maintain cardiac output

carotid sinuses
: small pockets near the base of the internal carotid arteries that are the locations of the baroreceptors and chemoreceptors that trigger a reflex that aids in the regulation of vascular homeostasis

circulatory shock
: also simply called shock; a life-threatening medical condition in which the circulatory system is unable to supply enough blood flow to provide adequate oxygen and other nutrients to the tissues to maintain cellular metabolism

hypertension
: chronic and persistent blood pressure measurements of 140/90 mm Hg or above

hypovolemic shock

type of circulatory shock caused by excessive loss of blood volume due to hemorrhage or possibly dehydration

myogenic response
: constriction or dilation in the walls of arterioles in response to pressures related to blood flow; reduces high blood flow or increases low blood flow to help maintain consistent flow to the capillary network

neurogenic shock
: type of shock that occurs with cranial or high spinal injuries that damage the cardiovascular centers in the medulla oblongata or the nervous fibers originating from this region

obstructive shock
: type of shock that occurs when a significant portion of the vascular system is blocked

sepsis
: (also, septicemia) organismal-level inflammatory response to a massive infection

septic shock
: (also, blood poisoning) type of shock that follows a massive infection resulting in organism-wide inflammation

vascular shock
: type of shock that occurs when arterioles lose their normal muscular tone and dilate dramatically

Anatomy of the Lymphatic and Immune Systems
By the end of this section, you will be able to:

- Describe the structure and function of the lymphatic tissue (lymph fluid, vessels, ducts, and organs)
- Describe the structure and function of the primary and secondary lymphatic organs
- Discuss the cells of the immune system, how they function, and their relationship with the lymphatic system

The **immune system** is the complex collection of cells and organs that destroys or neutralizes pathogens that would otherwise cause disease or death. The lymphatic system, for most people, is associated with the immune system to such a degree that the two systems are virtually indistinguishable. The **lymphatic system** is the system of vessels, cells, and organs that carries excess fluids to the bloodstream and filters pathogens from the blood. The swelling of lymph nodes during an infection and the transport of lymphocytes via the lymphatic vessels are but two examples of the many connections between these critical organ systems.

Functions of the Lymphatic System

A major function of the lymphatic system is to drain body fluids and return them to the bloodstream. Blood pressure causes leakage of fluid from the capillaries, resulting in the accumulation of fluid in the interstitial space—that is, spaces between individual cells in the tissues. In humans, 20 liters of plasma is released into the interstitial space of the tissues each day due to capillary filtration. Once this filtrate is out of the bloodstream and in the tissue spaces, it is referred to as interstitial fluid. Of this, 17 liters is reabsorbed directly by the blood vessels. But what happens to the remaining three liters? This is where the lymphatic system comes into play. It drains the excess fluid and empties it back into the bloodstream via a series of vessels, trunks, and ducts. **Lymph** is the term used to describe interstitial fluid once it has entered the lymphatic system. When the lymphatic system is damaged in some way, such as by being blocked by cancer cells or destroyed by injury, protein-rich interstitial fluid accumulates (sometimes "backs up" from the lymph vessels) in the tissue spaces. This inappropriate

accumulation of fluid referred to as lymphedema may lead to serious medical consequences.

As the vertebrate immune system evolved, the network of lymphatic vessels became convenient avenues for transporting the cells of the immune system. Additionally, the transport of dietary lipids and fat-soluble vitamins absorbed in the gut uses this system.

Cells of the immune system not only use lymphatic vessels to make their way from interstitial spaces back into the circulation, but they also use lymph nodes as major staging areas for the development of critical immune responses. A **lymph node** is one of the small, bean-shaped organs located throughout the lymphatic system.

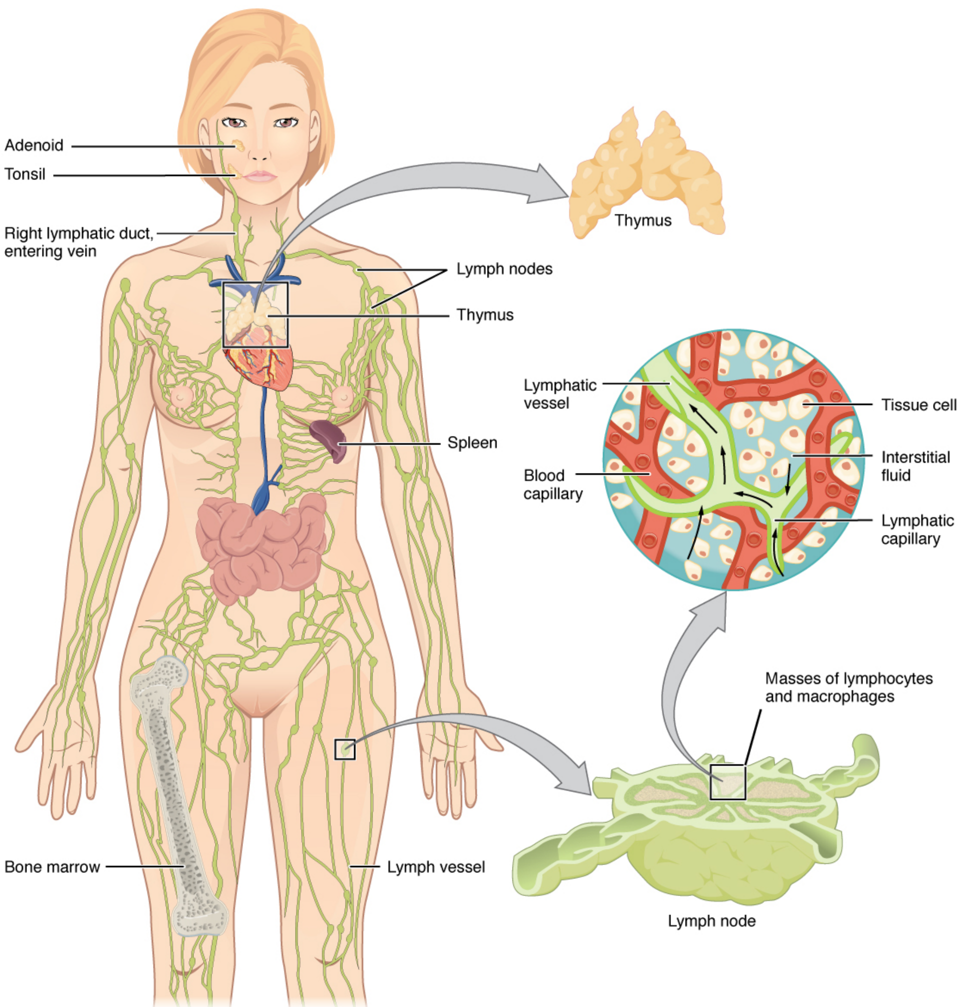
Note:

Visit this website for an overview of the lymphatic system. What are the three main components of the lymphatic system?

Structure of the Lymphatic System

The lymphatic vessels begin as open-ended capillaries, which feed into larger and larger lymphatic vessels, and eventually empty into the bloodstream by a series of ducts. Along the way, the lymph travels through the lymph nodes, which are commonly found near the groin, armpits, neck, chest, and abdomen. Humans have about 500–600 lymph nodes throughout the body ([link]).

Anatomy of the Lymphatic System



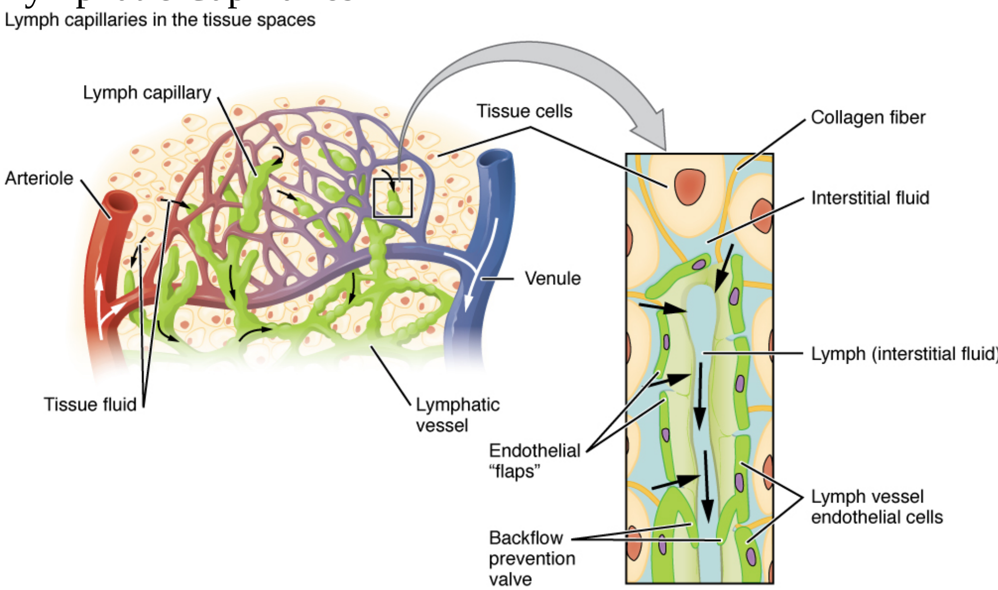
Lymphatic vessels in the arms and legs convey lymph to the larger lymphatic vessels in the torso.

A major distinction between the lymphatic and cardiovascular systems in humans is that lymph is not actively pumped by the heart, but is forced through the vessels by the movements of the body, the contraction of skeletal muscles during body movements, and breathing. One-way valves (semi-lunar valves) in lymphatic vessels keep the lymph moving toward the heart. Lymph flows from the lymphatic capillaries, through lymphatic vessels, and then is dumped into the circulatory system via the lymphatic ducts located at the junction of the jugular and subclavian veins in the neck.

Lymphatic Capillaries

Lymphatic capillaries, also called the terminal lymphatics, are vessels where interstitial fluid enters the lymphatic system to become lymph fluid. Located in almost every tissue in the body, these vessels are interlaced among the arterioles and venules of the circulatory system in the soft connective tissues of the body ([link]). Exceptions are the central nervous system, bone marrow, bones, teeth, and the cornea of the eye, which do not contain lymph vessels.

Lymphatic Capillaries



Lymphatic capillaries are interlaced with the arterioles and venules of the cardiovascular system. Collagen fibers anchor a lymphatic capillary in the tissue (inset). Interstitial fluid slips through spaces between the overlapping endothelial cells that compose the lymphatic capillary.

Lymphatic capillaries are formed by a one cell-thick layer of endothelial cells and represent the open end of the system, allowing interstitial fluid to flow into them via overlapping cells (see [link]). When interstitial pressure is low, the endothelial flaps close to prevent "backflow." As interstitial pressure increases, the spaces between the cells open up, allowing the fluid

to enter. Entry of fluid into lymphatic capillaries is also enabled by the collagen filaments that anchor the capillaries to surrounding structures. As interstitial pressure increases, the filaments pull on the endothelial cell flaps, opening up them even further to allow easy entry of fluid.

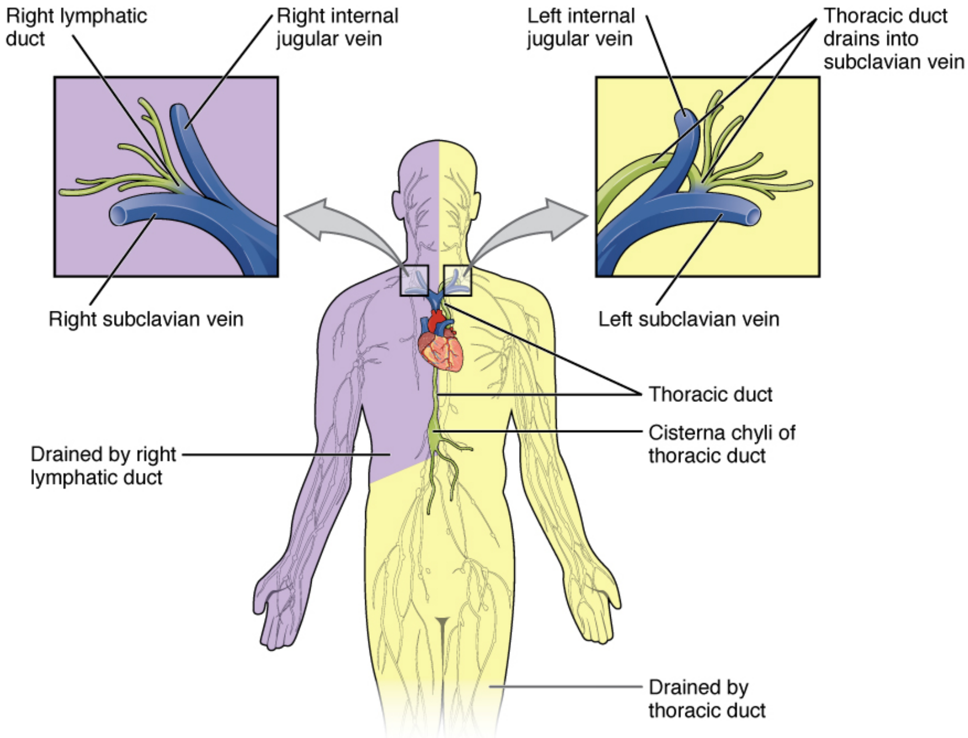
In the small intestine, lymphatic capillaries called lacteals are critical for the transport of dietary lipids and lipid-soluble vitamins to the bloodstream. In the small intestine, dietary triglycerides combine with other lipids and proteins, and enter the lacteals to form a milky fluid called **chyle**. The chyle then travels through the lymphatic system, eventually entering the bloodstream.

Larger Lymphatic Vessels, Trunks, and Ducts

The lymphatic capillaries empty into larger lymphatic vessels, which are similar to veins in terms of their three-tunic structure and the presence of valves. These one-way valves are located fairly close to one another, and each one causes a bulge in the lymphatic vessel, giving the vessels a beaded appearance (see [link]).

The superficial and deep lymphatics eventually merge to form larger lymphatic vessels known as **lymphatic trunks**. On the right side of the body, the right sides of the head, thorax, and right upper limb drain lymph fluid into the right subclavian vein via the right lymphatic duct ([link]). On the left side of the body, the remaining portions of the body drain into the larger thoracic duct, which drains into the left subclavian vein. The thoracic duct itself begins just beneath the diaphragm in the **cisterna chyli**, a sac-like chamber that receives lymph from the lower abdomen, pelvis, and lower limbs by way of the left and right lumbar trunks and the intestinal trunk.

Major Trunks and Ducts of the Lymphatic System



The thoracic duct drains a much larger portion of the body than does the right lymphatic duct.

The overall drainage system of the body is asymmetrical (see [link]). The **right lymphatic duct** receives lymph from only the upper right side of the body. The lymph from the rest of the body enters the bloodstream through the **thoracic duct** via all the remaining lymphatic trunks. In general, lymphatic vessels of the subcutaneous tissues of the skin, that is, the superficial lymphatics, follow the same routes as veins, whereas the deep lymphatic vessels of the viscera generally follow the paths of arteries.

The Organization of Immune Function

The immune system is a collection of barriers, cells, and soluble proteins that interact and communicate with each other in extraordinarily complex ways. The modern model of immune function is organized into three phases

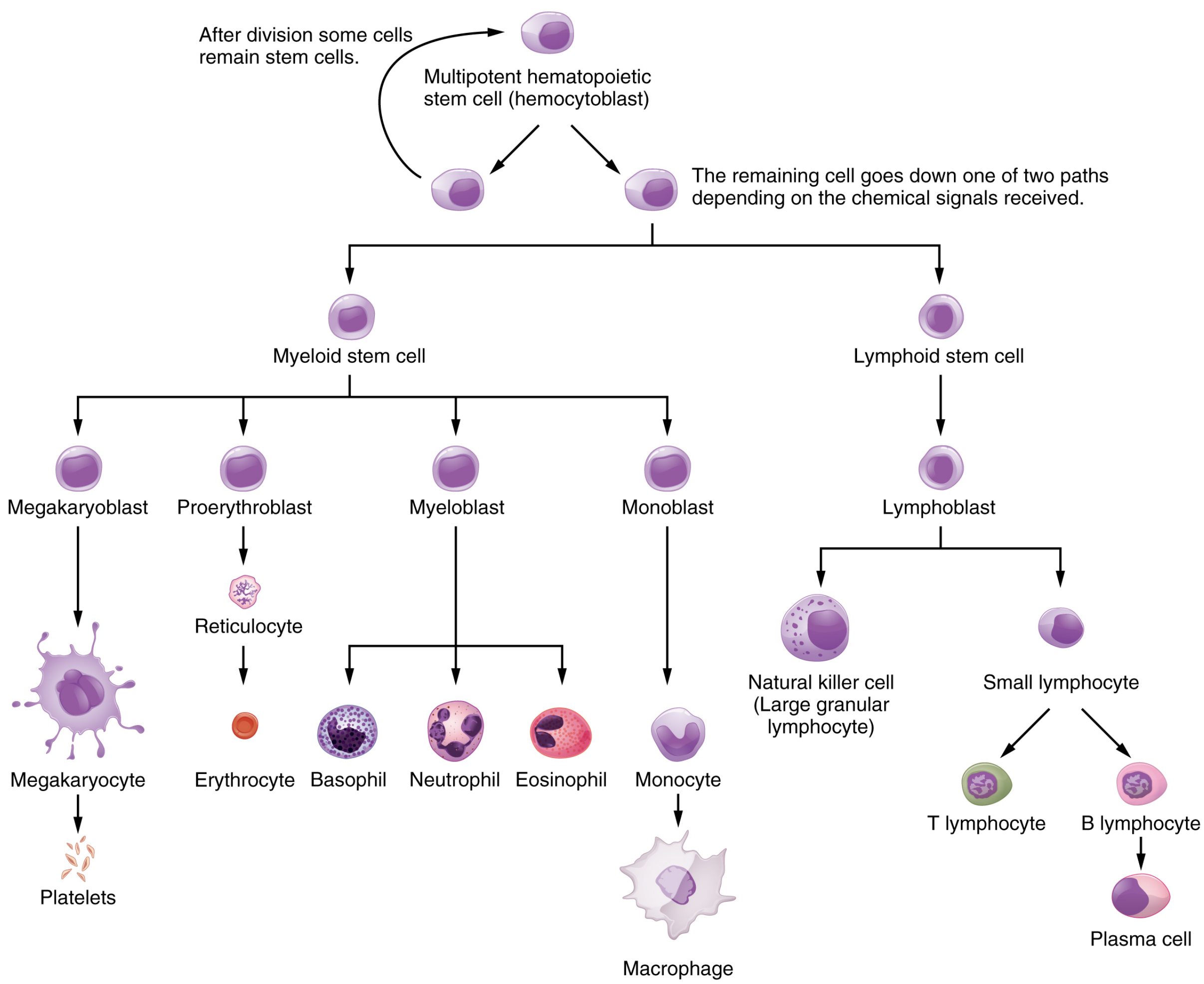
based on the timing of their effects. The three temporal phases consist of the following:

- **Barrier defenses** such as the skin and mucous membranes, which act instantaneously to prevent pathogenic invasion into the body tissues
- The rapid but nonspecific **innate immune response**, which consists of a variety of specialized cells and soluble factors
- The slower but more specific and effective **adaptive immune response**, which involves many cell types and soluble factors, but is primarily controlled by white blood cells (leukocytes) known as **lymphocytes**, which help control immune responses

The cells of the blood, including all those involved in the immune response, arise in the bone marrow via various differentiation pathways from hematopoietic stem cells ([link]). In contrast with embryonic stem cells, hematopoietic stem cells are present throughout adulthood and allow for the continuous differentiation of blood cells to replace those lost to age or function. These cells can be divided into three classes based on function:

- Phagocytic cells, which ingest pathogens to destroy them
- Lymphocytes, which specifically coordinate the activities of adaptive immunity
- Cells containing cytoplasmic granules, which help mediate immune responses against parasites and intracellular pathogens such as viruses

Hematopoietic System of the Bone Marrow



All the cells of the immune response as well as of the blood arise by differentiation from hematopoietic stem cells. Platelets are cell fragments involved in the clotting of blood.

Lymphocytes: B Cells, T Cells, Plasma Cells, and Natural Killer Cells

As stated above, lymphocytes are the primary cells of adaptive immune responses ([link]). The two basic types of lymphocytes, B cells and T cells, are identical morphologically with a large central nucleus surrounded by a thin layer of cytoplasm. They are distinguished from each other by their surface protein markers as well as by the molecules they secrete. While B

cells mature in red bone marrow and T cells mature in the thymus, they both initially develop from bone marrow. T cells migrate from bone marrow to the thymus gland where they further mature. B cells and T cells are found in many parts of the body, circulating in the bloodstream and lymph, and residing in secondary lymphoid organs, including the spleen and lymph nodes, which will be described later in this section. The human body contains approximately 10^{12} lymphocytes.

B Cells

B cells are immune cells that function primarily by producing antibodies. An **antibody** is any of the group of proteins that binds specifically to pathogen-associated molecules known as antigens. An **antigen** is a chemical structure on the surface of a pathogen that binds to T or B lymphocyte antigen receptors. Once activated by binding to antigen, B cells differentiate into cells that secrete a soluble form of their surface antibodies. These activated B cells are known as plasma cells.

T Cells

The **T cell**, on the other hand, does not secrete antibody but performs a variety of functions in the adaptive immune response. Different T cell types have the ability to either secrete soluble factors that communicate with other cells of the adaptive immune response or destroy cells infected with intracellular pathogens. The roles of T and B lymphocytes in the adaptive immune response will be discussed further in this chapter.

Plasma Cells

Another type of lymphocyte of importance is the plasma cell. A **plasma cell** is a B cell that has differentiated in response to antigen binding, and has thereby gained the ability to secrete soluble antibodies. These cells differ in morphology from standard B and T cells in that they contain a large amount

of cytoplasm packed with the protein-synthesizing machinery known as rough endoplasmic reticulum.

Natural Killer Cells

A fourth important lymphocyte is the natural killer cell, a participant in the innate immune response. A **natural killer cell (NK)** is a circulating blood cell that contains cytotoxic (cell-killing) granules in its extensive cytoplasm. It shares this mechanism with the cytotoxic T cells of the adaptive immune response. NK cells are among the body's first lines of defense against viruses and certain types of cancer.

Lymphocytes	
Type of lymphocyte	**Primary function**
B lymphocyte	Generates diverse antibodies
T lymphocyte	Secretes chemical messengers
Plasma cell	Secretes antibodies
NK cell	Destroys virally infected cells

Note:

Visit this website to learn about the many different cell types in the immune system and their very specialized jobs. What is the role of the dendritic cell in an HIV infection?

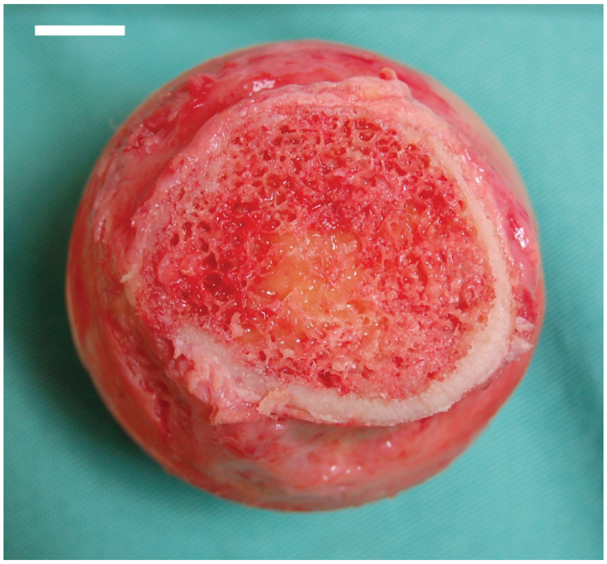
Primary Lymphoid Organs and Lymphocyte Development

Understanding the differentiation and development of B and T cells is critical to the understanding of the adaptive immune response. It is through this process that the body (ideally) learns to destroy only pathogens and leaves the body’s own cells relatively intact. The **primary lymphoid organs** are the bone marrow and thymus gland. The lymphoid organs are where lymphocytes mature, proliferate, and are selected, which enables them to attack pathogens without harming the cells of the body.

Bone Marrow

In the embryo, blood cells are made in the yolk sac. As development proceeds, this function is taken over by the spleen, lymph nodes, and liver. Later, the bone marrow takes over most hematopoietic functions, although the final stages of the differentiation of some cells may take place in other organs. The red **bone marrow** is a loose collection of cells where hematopoiesis occurs, and the yellow bone marrow is a site of energy storage, which consists largely of fat cells ([link]). The B cell undergoes nearly all of its development in the red bone marrow, whereas the immature T cell, called a **thymocyte**, leaves the bone marrow and matures largely in the thymus gland.

Bone Marrow

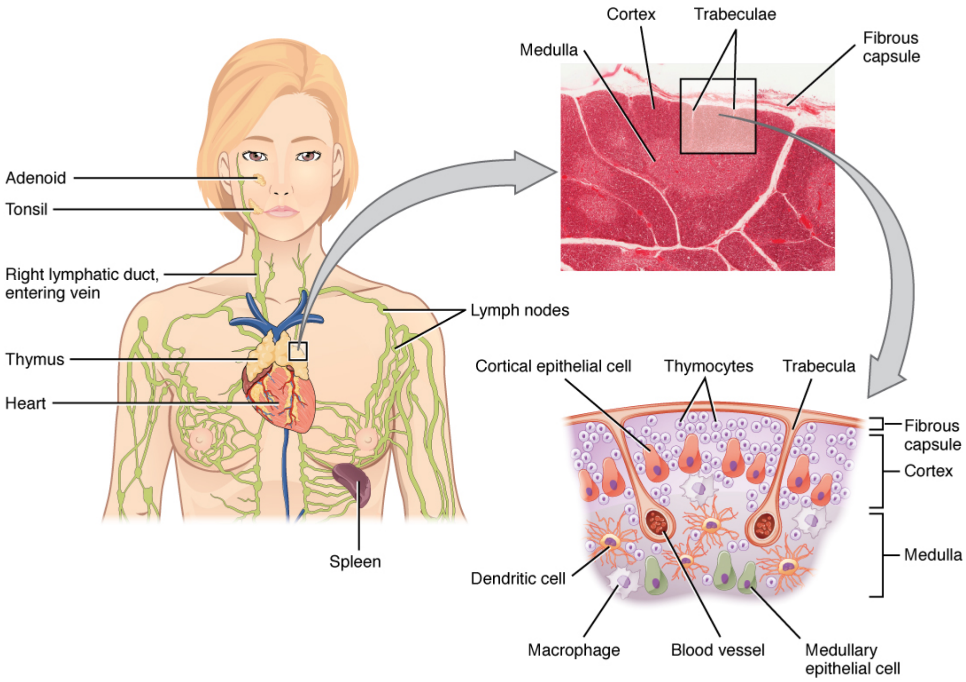


Red bone marrow fills the head of the femur, and a spot of yellow bone marrow is visible in the center. The white reference bar is 1 cm.

Thymus

The **thymus** gland is a bilobed organ found in the space between the sternum and the aorta of the heart ([link]). Connective tissue holds the lobes closely together but also separates them and forms a capsule.

Location, Structure, and Histology of the Thymus



The thymus lies above the heart. The trabeculae and lobules, including the darkly staining cortex and the lighter staining medulla of each lobule, are clearly visible in the light micrograph of the thymus of a newborn. LM × 100. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

Note:

View the University of Michigan WebScope to explore the tissue sample in greater detail.

The connective tissue capsule further divides the thymus into lobules via extensions called trabeculae. The outer region of the organ is known as the cortex and contains large numbers of thymocytes with some epithelial cells, macrophages, and dendritic cells (two types of phagocytic cells that are derived from monocytes). The cortex is densely packed so it stains more intensely than the rest of the thymus (see [link]). The medulla, where thymocytes migrate before leaving the thymus, contains a less dense collection of thymocytes, epithelial cells, and dendritic cells.

Note:
Aging and the…
Immune System
By the year 2050, 25 percent of the population of the United States will be 60 years of age or older. The CDC estimates that 80 percent of those 60 years and older have one or more chronic disease associated with deficiencies of the immune systems. This loss of immune function with age is called immunosenescence. To treat this growing population, medical professionals must better understand the aging process. One major cause of age-related immune deficiencies is thymic involution, the shrinking of the thymus gland that begins at birth, at a rate of about three percent tissue loss per year, and continues until 35–45 years of age, when the rate declines to about one percent loss per year for the rest of one's life. At that pace, the total loss of thymic epithelial tissue and thymocytes would occur at about 120 years of age. Thus, this age is a theoretical limit to a healthy human lifespan.
Thymic involution has been observed in all vertebrate species that have a thymus gland. Animal studies have shown that transplanted thymic grafts between inbred strains of mice involuted according to the age of the donor and not of the recipient, implying the process is genetically programmed. There is evidence that the thymic microenvironment, so vital to the

development of naïve T cells, loses thymic epithelial cells according to the decreasing expression of the FOXN1 gene with age.
It is also known that thymic involution can be altered by hormone levels. Sex hormones such as estrogen and testosterone enhance involution, and the hormonal changes in pregnant women cause a temporary thymic involution that reverses itself, when the size of the thymus and its hormone levels return to normal, usually after lactation ceases. What does all this tell us? Can we reverse immunosenescence, or at least slow it down? The potential is there for using thymic transplants from younger donors to keep thymic output of naïve T cells high. Gene therapies that target gene expression are also seen as future possibilities. The more we learn through immunosenescence research, the more opportunities there will be to develop therapies, even though these therapies will likely take decades to develop. The ultimate goal is for everyone to live and be healthy longer, but there may be limits to immortality imposed by our genes and hormones.

Secondary Lymphoid Organs and their Roles in Active Immune Responses

Lymphocytes develop and mature in the primary lymphoid organs, but they mount immune responses from the **secondary lymphoid organs**. A **naïve lymphocyte** is one that has left the primary organ and entered a secondary lymphoid organ. Naïve lymphocytes are fully functional immunologically, but have yet to encounter an antigen to respond to. In addition to circulating in the blood and lymph, lymphocytes concentrate in secondary lymphoid organs, which include the lymph nodes, spleen, and lymphoid nodules. All of these tissues have many features in common, including the following:

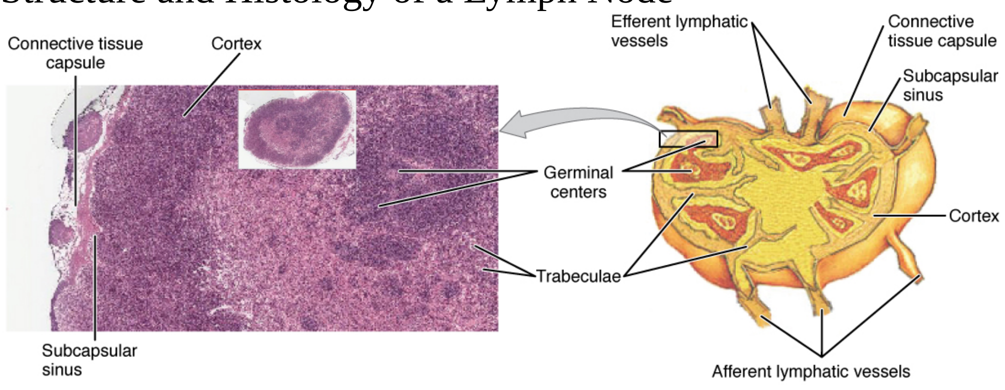
- The presence of lymphoid follicles, the sites of the formation of lymphocytes, with specific B cell-rich and T cell-rich areas
- An internal structure of reticular fibers with associated fixed macrophages
- **Germinal centers**, which are the sites of rapidly dividing and differentiating B lymphocytes

- Specialized post-capillary vessels known as **high endothelial venules**; the cells lining these venules are thicker and more columnar than normal endothelial cells, which allow cells from the blood to directly enter these tissues

Lymph Nodes

Lymph nodes function to remove debris and pathogens from the lymph, and are thus sometimes referred to as the “filters of the lymph” ([link]). Any bacteria that infect the interstitial fluid are taken up by the lymphatic capillaries and transported to a regional lymph node. Dendritic cells and macrophages within this organ internalize and kill many of the pathogens that pass through, thereby removing them from the body. The lymph node is also the site of adaptive immune responses mediated by T cells, B cells, and accessory cells of the adaptive immune system. Like the thymus, the bean-shaped lymph nodes are surrounded by a tough capsule of connective tissue and are separated into compartments by trabeculae, the extensions of the capsule. In addition to the structure provided by the capsule and trabeculae, the structural support of the lymph node is provided by a series of reticular fibers laid down by fibroblasts.

Structure and Histology of a Lymph Node



Lymph nodes are masses of lymphatic tissue located along the larger lymph vessels. The micrograph of the lymph nodes shows a germinal center, which consists of rapidly dividing B cells surrounded by a layer of T cells and other accessory cells. LM × 128. (Micrograph

provided by the Regents of the University of Michigan Medical School © 2012)

Note:

View the University of Michigan WebScope to explore the tissue sample in greater detail.

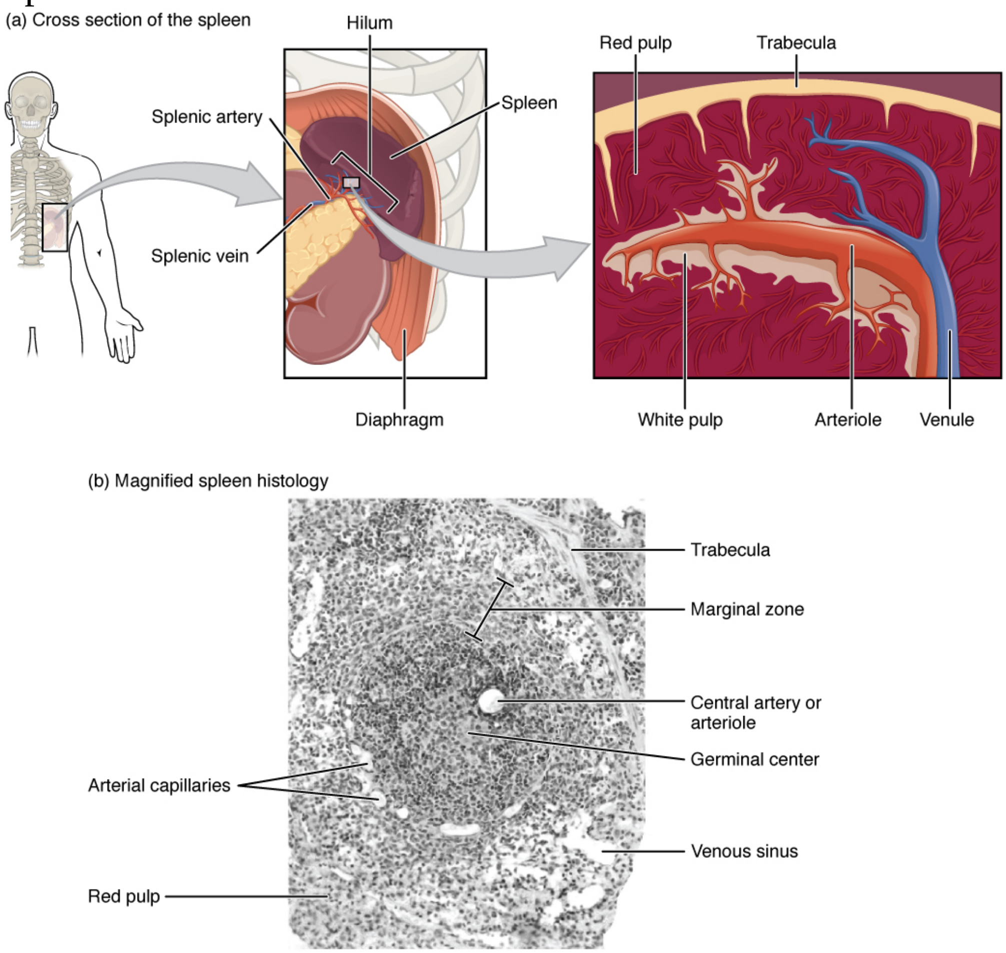
The major routes into the lymph node are via **afferent lymphatic vessels** (see [link]). Cells and lymph fluid that leave the lymph node may do so by another set of vessels known as the **efferent lymphatic vessels**. Lymph enters the lymph node via the subcapsular sinus, which is occupied by dendritic cells, macrophages, and reticular fibers. Within the cortex of the lymph node are lymphoid follicles, which consist of germinal centers of rapidly dividing B cells surrounded by a layer of T cells and other accessory cells. As the lymph continues to flow through the node, it enters the medulla, which consists of medullary cords of B cells and plasma cells, and the medullary sinuses where the lymph collects before leaving the node via the efferent lymphatic vessels.

Spleen

In addition to the lymph nodes, the **spleen** is a major secondary lymphoid organ ([link]). It is about 12 cm (5 in) long and is attached to the lateral

border of the stomach via the gastrosplenic ligament. The spleen is a fragile organ without a strong capsule, and is dark red due to its extensive vascularization. The spleen is sometimes called the “filter of the blood” because of its extensive vascularization and the presence of macrophages and dendritic cells that remove microbes and other materials from the blood, including dying red blood cells. The spleen also functions as the location of immune responses to blood-borne pathogens.

Spleen



(a) The spleen is attached to the stomach. (b) A micrograph of spleen tissue shows the germinal center. The marginal zone is the region between the red pulp and white pulp, which sequesters particulate antigens from the circulation and presents these antigens to lymphocytes in the white pulp. EM × 660. (Micrograph

provided by the Regents of the University of Michigan Medical School © 2012)

The spleen is also divided by trabeculae of connective tissue, and within each splenic nodule is an area of red pulp, consisting of mostly red blood cells, and white pulp, which resembles the lymphoid follicles of the lymph nodes. Upon entering the spleen, the splenic artery splits into several arterioles (surrounded by white pulp) and eventually into sinusoids. Blood from the capillaries subsequently collects in the venous sinuses and leaves via the splenic vein. The red pulp consists of reticular fibers with fixed macrophages attached, free macrophages, and all of the other cells typical of the blood, including some lymphocytes. The white pulp surrounds a central arteriole and consists of germinal centers of dividing B cells surrounded by T cells and accessory cells, including macrophages and dendritic cells. Thus, the red pulp primarily functions as a filtration system of the blood, using cells of the relatively nonspecific immune response, and white pulp is where adaptive T and B cell responses are mounted.

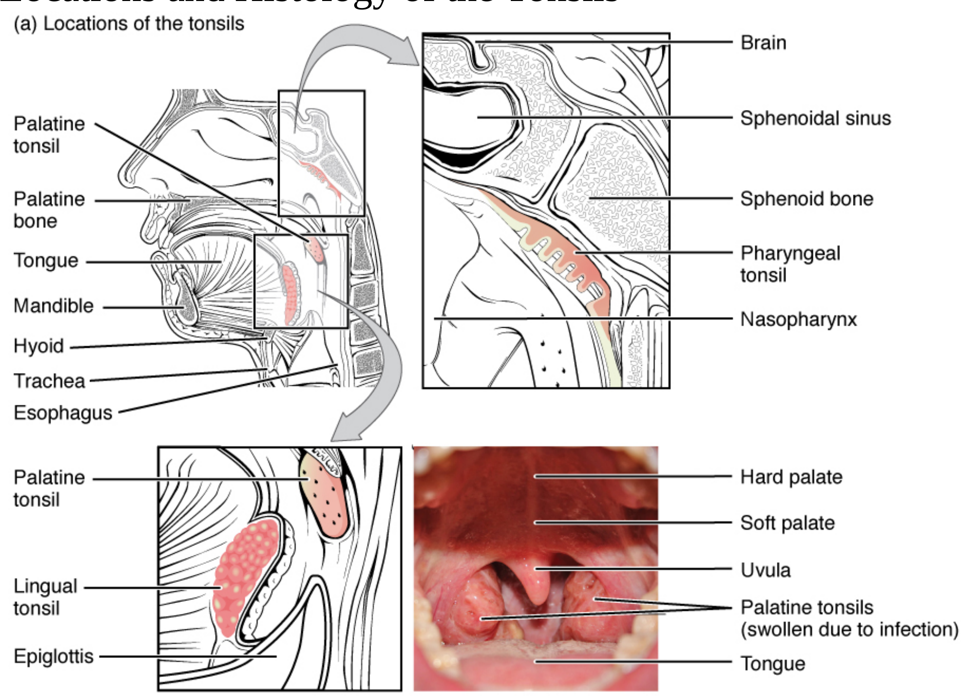
Lymphoid Nodules

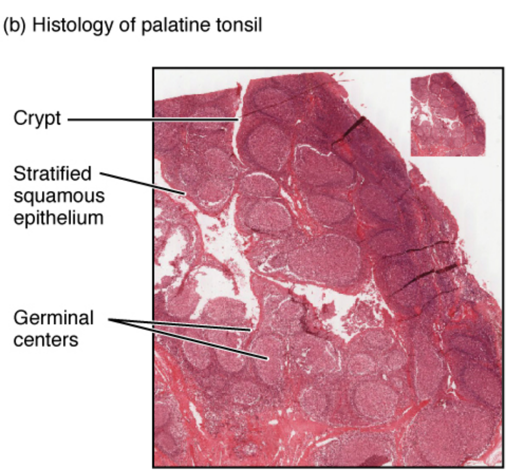
The other lymphoid tissues, the **lymphoid nodules**, have a simpler architecture than the spleen and lymph nodes in that they consist of a dense cluster of lymphocytes without a surrounding fibrous capsule. These nodules are located in the respiratory and digestive tracts, areas routinely exposed to environmental pathogens.

Tonsils are lymphoid nodules located along the inner surface of the pharynx and are important in developing immunity to oral pathogens ([link]). The tonsil located at the back of the throat, the pharyngeal tonsil, is sometimes referred to as the adenoid when swollen. Such swelling is an indication of an active immune response to infection. Histologically, tonsils do not contain a complete capsule, and the epithelial layer invaginates deeply into the interior of the tonsil to form tonsillar crypts. These structures, which accumulate all sorts of materials taken into the body through eating and breathing, actually “encourage” pathogens to penetrate deep into the

tonsillar tissues where they are acted upon by numerous lymphoid follicles and eliminated. This seems to be the major function of tonsils—to help children’s bodies recognize, destroy, and develop immunity to common environmental pathogens so that they will be protected in their later lives. Tonsils are often removed in those children who have recurring throat infections, especially those involving the palatine tonsils on either side of the throat, whose swelling may interfere with their breathing and/or swallowing.

Locations and Histology of the Tonsils





(a) The pharyngeal tonsil is located on the roof of the posterior superior wall of the nasopharynx. The palatine tonsils lay on each side of the pharynx. (b) A micrograph shows the palatine tonsil tissue. LM × 40. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

Note:

View the University of Michigan WebScope to explore the tissue sample in greater detail.

Mucosa-associated lymphoid tissue (MALT) consists of an aggregate of lymphoid follicles directly associated with the mucous membrane epithelia. MALT makes up dome-shaped structures found underlying the mucosa of the gastrointestinal tract, breast tissue, lungs, and eyes. Peyer's patches, a type of MALT in the small intestine, are especially important for immune responses against ingested substances ([link]). Peyer's patches contain specialized endothelial cells called M (or microfold) cells that sample material from the intestinal lumen and transport it to nearby follicles so that adaptive immune responses to potential pathogens can be mounted.

Mucosa-associated Lymphoid Tissue (MALT) Nodule

LM × 40. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

Bronchus-associated lymphoid tissue (BALT) consists of lymphoid follicular structures with an overlying epithelial layer found along the bifurcations of the bronchi, and between bronchi and arteries. They also have the typically less-organized structure of other lymphoid nodules. These tissues, in addition to the tonsils, are effective against inhaled pathogens.

Chapter Review

The lymphatic system is a series of vessels, ducts, and trunks that remove interstitial fluid from the tissues and return it the blood. The lymphatics are also used to transport dietary lipids and cells of the immune system. Cells of the immune system all come from the hematopoietic system of the bone marrow. Primary lymphoid organs, the bone marrow and thymus gland, are the locations where lymphocytes of the adaptive immune system proliferate and mature. Secondary lymphoid organs are site in which mature

lymphocytes congregate to mount immune responses. Many immune system cells use the lymphatic and circulatory systems for transport throughout the body to search for and then protect against pathogens.

Interactive Link Questions

Exercise:

Problem:

Visit this website for an overview of the lymphatic system. What are the three main components of the lymphatic system?

Solution:

The three main components are the lymph vessels, the lymph nodes, and the lymph.

Exercise:

Problem:

Visit this website to learn about the many different cell types in the immune system and their very specialized jobs. What is the role of the dendritic cell in infection by HIV?

Solution:

The dendritic cell transports the virus to a lymph node.

Review Questions

Exercise:

Problem: Which of the following cells is phagocytic?

a. plasma cell
b. macrophage

c. B cell
d. NK cell

Solution:

B

Exercise:

Problem:

Which structure allows lymph from the lower right limb to enter the bloodstream?

a. thoracic duct
b. right lymphatic duct
c. right lymphatic trunk
d. left lymphatic trunk

Solution:

A

Exercise:

Problem:

Which of the following cells is important in the innate immune response?

a. B cells
b. T cells
c. macrophages
d. plasma cells

Solution:

C

Exercise:

Problem:

Which of the following cells would be most active in early, antiviral immune responses the first time one is exposed to pathogen?

a. macrophage
b. T cell
c. neutrophil
d. natural killer cell

Solution:

D

Exercise:

Problem:

Which of the lymphoid nodules is most likely to see food antigens first?

a. tonsils
b. Peyer’s patches
c. bronchus-associated lymphoid tissue
d. mucosa-associated lymphoid tissue

Solution:

A

Critical Thinking Questions

Exercise:

Problem:

Describe the flow of lymph from its origins in interstitial fluid to its emptying into the venous bloodstream.

Solution:

The lymph enters through lymphatic capillaries, and then into larger lymphatic vessels. The lymph can only go in one direction due to valves in the vessels. The larger lymphatics merge to form trunks that enter into the blood via lymphatic ducts.

Glossary

adaptive immune response
: relatively slow but very specific and effective immune response controlled by lymphocytes

afferent lymphatic vessels
: lead into a lymph node

antibody
: antigen-specific protein secreted by plasma cells; immunoglobulin

antigen
: molecule recognized by the receptors of B and T lymphocytes

barrier defenses
: antipathogen defenses deriving from a barrier that physically prevents pathogens from entering the body to establish an infection

B cells
: lymphocytes that act by differentiating into an antibody-secreting plasma cell

bone marrow

tissue found inside bones; the site of all blood cell differentiation and maturation of B lymphocytes

bronchus-associated lymphoid tissue (BALT)
lymphoid nodule associated with the respiratory tract

chyle
lipid-rich lymph inside the lymphatic capillaries of the small intestine

cisterna chyli
bag-like vessel that forms the beginning of the thoracic duct

efferent lymphatic vessels
lead out of a lymph node

germinal centers
clusters of rapidly proliferating B cells found in secondary lymphoid tissues

high endothelial venules
vessels containing unique endothelial cells specialized to allow migration of lymphocytes from the blood to the lymph node

immune system
series of barriers, cells, and soluble mediators that combine to response to infections of the body with pathogenic organisms

innate immune response
rapid but relatively nonspecific immune response

lymph
fluid contained within the lymphatic system

lymph node
one of the bean-shaped organs found associated with the lymphatic vessels

lymphatic capillaries
smallest of the lymphatic vessels and the origin of lymph flow

lymphatic system
    network of lymphatic vessels, lymph nodes, and ducts that carries lymph from the tissues and back to the bloodstream.

lymphatic trunks
    large lymphatics that collect lymph from smaller lymphatic vessels and empties into the blood via lymphatic ducts

lymphocytes
    white blood cells characterized by a large nucleus and small rim of cytoplasm

lymphoid nodules
    unencapsulated patches of lymphoid tissue found throughout the body

mucosa-associated lymphoid tissue (MALT)
    lymphoid nodule associated with the mucosa

naïve lymphocyte
    mature B or T cell that has not yet encountered antigen for the first time

natural killer cell (NK)
    cytotoxic lymphocyte of innate immune response

plasma cell
    differentiated B cell that is actively secreting antibody

primary lymphoid organ
    site where lymphocytes mature and proliferate; red bone marrow and thymus gland

right lymphatic duct
    drains lymph fluid from the upper right side of body into the right subclavian vein

secondary lymphoid organs

sites where lymphocytes mount adaptive immune responses; examples include lymph nodes and spleen

spleen
: secondary lymphoid organ that filters pathogens from the blood (white pulp) and removes degenerating or damaged blood cells (red pulp)

T cell
: lymphocyte that acts by secreting molecules that regulate the immune system or by causing the destruction of foreign cells, viruses, and cancer cells

thoracic duct
: large duct that drains lymph from the lower limbs, left thorax, left upper limb, and the left side of the head

thymocyte
: immature T cell found in the thymus

thymus
: primary lymphoid organ; where T lymphocytes proliferate and mature

tonsils
: lymphoid nodules associated with the nasopharynx

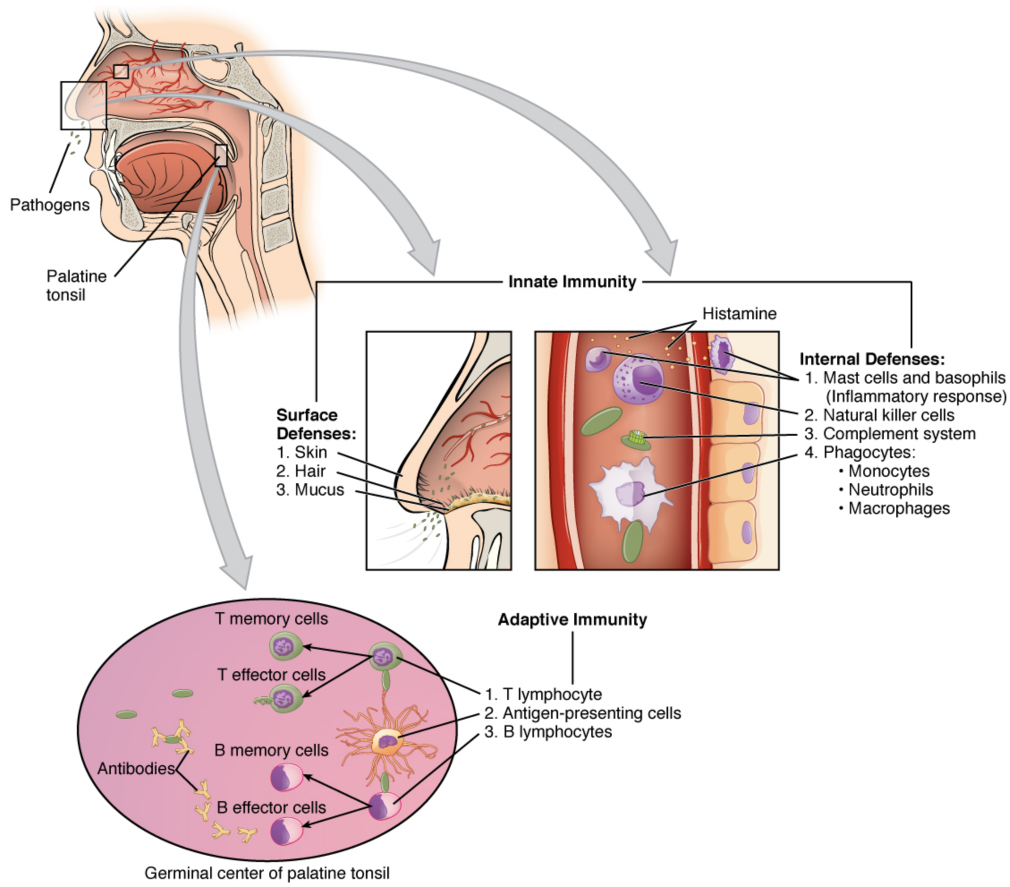
Barrier Defenses and the Innate Immune Response

By the end of this section, you will be able to:

- Describe the barrier defenses of the body
- Show how the innate immune response is important and how it helps guide and prepare the body for adaptive immune responses
- Describe various soluble factors that are part of the innate immune response
- Explain the steps of inflammation and how they lead to destruction of a pathogen
- Discuss early induced immune responses and their level of effectiveness

The immune system can be divided into two overlapping mechanisms to destroy pathogens: the innate immune response, which is relatively rapid but nonspecific and thus not always effective, and the adaptive immune response, which is slower in its development during an initial infection with a pathogen, but is highly specific and effective at attacking a wide variety of pathogens ([link]).

Cooperation between Innate and Adaptive Immune Responses



The innate immune system enhances adaptive immune responses so they can be more effective.

Any discussion of the innate immune response usually begins with the physical barriers that prevent pathogens from entering the body, destroy them after they enter, or flush them out before they can establish themselves in the hospitable environment of the body's soft tissues. Barrier defenses are part of the body's most basic defense mechanisms. The barrier defenses are not a response to infections, but they are continuously working to protect against a broad range of pathogens.

The different modes of barrier defenses are associated with the external surfaces of the body, where pathogens may try to enter ([link]). The primary barrier to the entrance of microorganisms into the body is the skin. Not only is the skin covered with a layer of dead, keratinized epithelium that is too dry for bacteria in which to grow, but as these cells are continuously sloughed off from the skin, they carry bacteria and other pathogens with them. Additionally, sweat and other skin secretions may lower pH, contain toxic lipids, and physically wash microbes away.

Barrier Defenses

Site	**Specific defense**	**Protective aspect**
Skin	Epidermal surface	Keratinized cells of surface, Langerhans cells
Skin (sweat/secretions)	Sweat glands, sebaceous glands	Low pH, washing action
Oral cavity	Salivary glands	Lysozyme
Stomach	Gastrointestinal tract	Low pH

Barrier Defenses		
Site	**Specific defense**	**Protective aspect**
Mucosal surfaces	Mucosal epithelium	Nonkeratinized epithelial cells
Normal flora (nonpathogenic bacteria)	Mucosal tissues	Prevent pathogens from growing on mucosal surfaces

Another barrier is the saliva in the mouth, which is rich in lysozyme—an enzyme that destroys bacteria by digesting their cell walls. The acidic environment of the stomach, which is fatal to many pathogens, is also a barrier. Additionally, the mucus layer of the gastrointestinal tract, respiratory tract, reproductive tract, eyes, ears, and nose traps both microbes and debris, and facilitates their removal. In the case of the upper respiratory tract, ciliated epithelial cells move potentially contaminated mucus upwards to the mouth, where it is then swallowed into the digestive tract, ending up in the harsh acidic environment of the stomach. Considering how often you breathe compared to how often you eat or perform other activities that expose you to pathogens, it is not surprising that multiple barrier mechanisms have evolved to work in concert to protect this vital area.

Cells of the Innate Immune Response

A phagocyte is a cell that is able to surround and engulf a particle or cell, a process called **phagocytosis**. The phagocytes of the immune system engulf other particles or cells, either to clean an area of debris, old cells, or to kill pathogenic organisms such as bacteria. The phagocytes are the body’s fast acting, first line of immunological defense against organisms that have breached barrier defenses and have entered the vulnerable tissues of the body.

Phagocytes: Macrophages and Neutrophils

Many of the cells of the immune system have a phagocytic ability, at least at some point during their life cycles. Phagocytosis is an important and effective mechanism of destroying pathogens during innate immune responses. The phagocyte takes the

organism inside itself as a phagosome, which subsequently fuses with a lysosome and its digestive enzymes, effectively killing many pathogens. On the other hand, some bacteria including *Mycobacteria tuberculosis*, the cause of tuberculosis, may be resistant to these enzymes and are therefore much more difficult to clear from the body. Macrophages, neutrophils, and dendritic cells are the major phagocytes of the immune system.

A **macrophage** is an irregularly shaped phagocyte that is amoeboid in nature and is the most versatile of the phagocytes in the body. Macrophages move through tissues and squeeze through capillary walls using pseudopodia. They not only participate in innate immune responses but have also evolved to cooperate with lymphocytes as part of the adaptive immune response. Macrophages exist in many tissues of the body, either freely roaming through connective tissues or fixed to reticular fibers within specific tissues such as lymph nodes. When pathogens breach the body's barrier defenses, macrophages are the first line of defense ([link]). They are called different names, depending on the tissue: Kupffer cells in the liver, histiocytes in connective tissue, and alveolar macrophages in the lungs.

A **neutrophil** is a phagocytic cell that is attracted via chemotaxis from the bloodstream to infected tissues. These spherical cells are granulocytes. A granulocyte contains cytoplasmic granules, which in turn contain a variety of vasoactive mediators such as histamine. In contrast, macrophages are agranulocytes. An agranulocyte has few or no cytoplasmic granules. Whereas macrophages act like sentries, always on guard against infection, neutrophils can be thought of as military reinforcements that are called into a battle to hasten the destruction of the enemy. Although, usually thought of as the primary pathogen-killing cell of the inflammatory process of the innate immune response, new research has suggested that neutrophils play a role in the adaptive immune response as well, just as macrophages do.

A **monocyte** is a circulating precursor cell that differentiates into either a macrophage or dendritic cell, which can be rapidly attracted to areas of infection by signal molecules of inflammation.

Phagocytic Cells of the Innate Immune System

Phagocytic Cells of the Innate Immune System			
Cell	**Cell type**	**Primary location**	**Function in the innate immune response**
Macrophage	Agranulocyte	Body cavities/organs	Phagocytosis
Neutrophil	Granulocyte	Blood	Phagocytosis
Monocyte	Agranulocyte	Blood	Precursor of macrophage/dendritic cell

Natural Killer Cells

NK cells are a type of lymphocyte that have the ability to induce apoptosis, that is, programmed cell death, in cells infected with intracellular pathogens such as obligate intracellular bacteria and viruses. NK cells recognize these cells by mechanisms that are still not well understood, but that presumably involve their surface receptors. NK cells can induce apoptosis, in which a cascade of events inside the cell causes its own death by either of two mechanisms:

1) NK cells are able to respond to chemical signals and express the fas ligand. The **fas ligand** is a surface molecule that binds to the fas molecule on the surface of the infected cell, sending it apoptotic signals, thus killing the cell and the pathogen within it; or

2) The granules of the NK cells release perforins and granzymes. A **perforin** is a protein that forms pores in the membranes of infected cells. A **granzyme** is a protein-digesting enzyme that enters the cell via the perforin pores and triggers apoptosis intracellularly.

Both mechanisms are especially effective against virally infected cells. If apoptosis is induced before the virus has the ability to synthesize and assemble all its components, no infectious virus will be released from the cell, thus preventing further infection.

Recognition of Pathogens

Cells of the innate immune response, the phagocytic cells, and the cytotoxic NK cells recognize patterns of pathogen-specific molecules, such as bacterial cell wall components or bacterial flagellar proteins, using pattern recognition receptors. A **pattern recognition receptor (PRR)** is a membrane-bound receptor that recognizes characteristic features of a pathogen and molecules released by stressed or damaged cells.

These receptors, which are thought to have evolved prior to the adaptive immune response, are present on the cell surface whether they are needed or not. Their variety, however, is limited by two factors. First, the fact that each receptor type must be encoded by a specific gene requires the cell to allocate most or all of its DNA to make receptors able to recognize all pathogens. Secondly, the variety of receptors is limited by the finite surface area of the cell membrane. Thus, the innate immune system must “get by” using only a limited number of receptors that are active against as wide a variety of pathogens as possible. This strategy is in stark contrast to the approach used by the adaptive immune system, which uses large numbers of different receptors, each highly specific to a particular pathogen.

Should the cells of the innate immune system come into contact with a species of pathogen they recognize, the cell will bind to the pathogen and initiate phagocytosis (or cellular apoptosis in the case of an intracellular pathogen) in an effort to destroy the offending microbe. Receptors vary somewhat according to cell type, but they usually include receptors for bacterial components and for complement, discussed below.

Soluble Mediators of the Innate Immune Response

The previous discussions have alluded to chemical signals that can induce cells to change various physiological characteristics, such as the expression of a particular receptor. These soluble factors are secreted during innate or early induced responses, and later during adaptive immune responses.

Cytokines and Chemokines

A **cytokine** is signaling molecule that allows cells to communicate with each other over short distances. Cytokines are secreted into the intercellular space, and the action of the cytokine induces the receiving cell to change its physiology. A **chemokine** is a soluble chemical mediator similar to cytokines except that its function is to attract cells (chemotaxis) from longer distances.

Note:

Visit this website to learn about phagocyte chemotaxis. Phagocyte chemotaxis is the movement of phagocytes according to the secretion of chemical messengers in the form of interleukins and other chemokines. By what means does a phagocyte destroy a bacterium that it has ingested?

Early induced Proteins

Early induced proteins are those that are not constitutively present in the body, but are made as they are needed early during the innate immune response. **Interferons** are an example of early induced proteins. Cells infected with viruses secrete interferons that travel to adjacent cells and induce them to make antiviral proteins. Thus, even though the initial cell is sacrificed, the surrounding cells are protected. Other early induced proteins specific for bacterial cell wall components are mannose-binding protein and C-reactive protein, made in the liver, which bind specifically to polysaccharide components of the bacterial cell wall. Phagocytes such as macrophages have receptors for these proteins, and they are thus able to recognize them as they are bound to the bacteria. This brings the phagocyte and bacterium into close proximity and enhances the phagocytosis of the bacterium by the process known as opsonization. **Opsonization** is the tagging of a pathogen for phagocytosis by the binding of an antibody or an antimicrobial protein.

Complement System

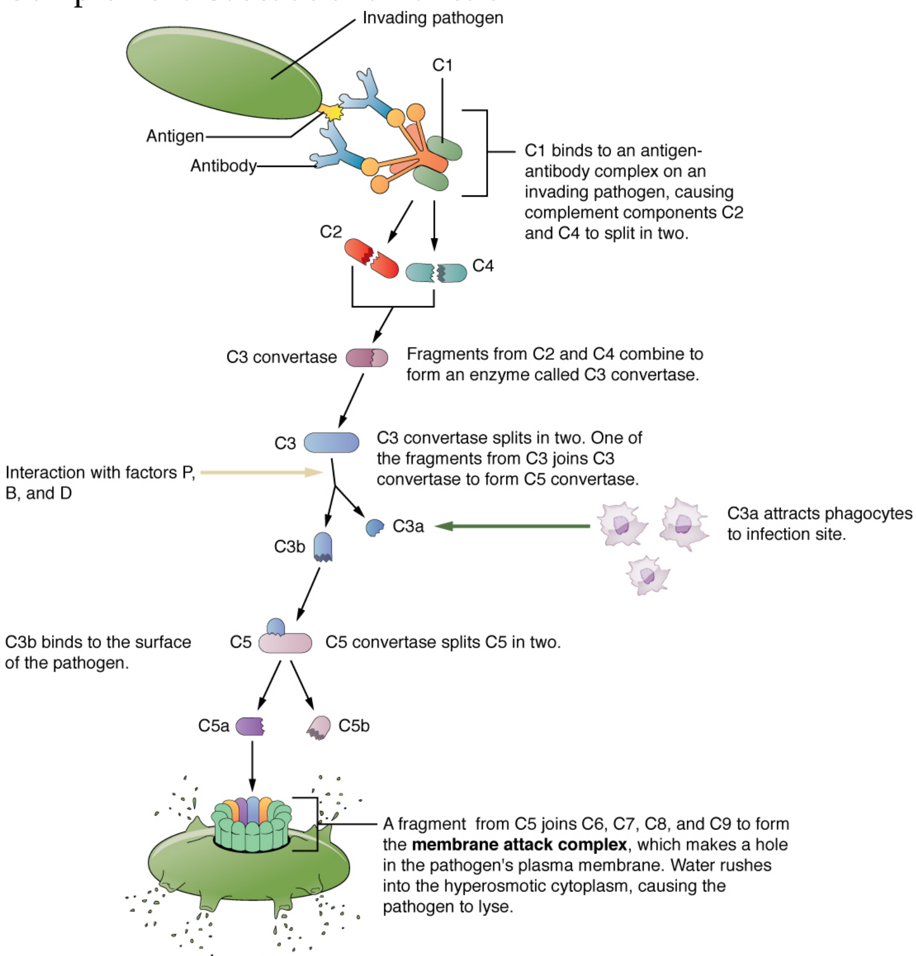
The **complement** system is a series of proteins constitutively found in the blood plasma. As such, these proteins are not considered part of the **early induced immune response**, even though they share features with some of the antibacterial proteins of this class. Made in the liver, they have a variety of functions in the innate immune response, using what is known as the “alternate pathway” of complement activation. Additionally, complement functions in the adaptive immune response as well, in what is called the classical pathway. The complement

system consists of several proteins that enzymatically alter and fragment later proteins in a series, which is why it is termed cascade. Once activated, the series of reactions is irreversible, and releases fragments that have the following actions:

- Bind to the cell membrane of the pathogen that activates it, labeling it for phagocytosis (opsonization)
- Diffuse away from the pathogen and act as chemotactic agents to attract phagocytic cells to the site of inflammation
- Form damaging pores in the plasma membrane of the pathogen

[link] shows the classical pathway, which requires antibodies of the adaptive immune response. The alternate pathway does not require an antibody to become activated.

Complement Cascade and Function

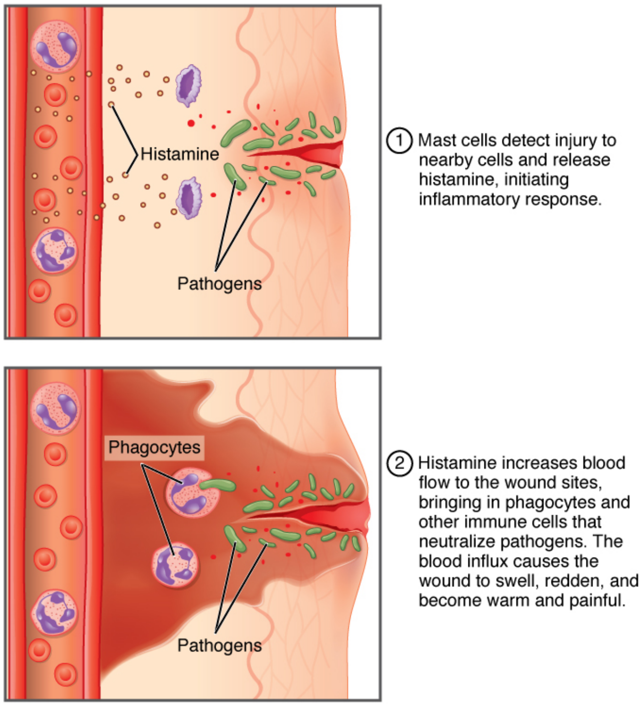


The classical pathway, used during adaptive immune responses, occurs when C1 reacts with antibodies that have bound an antigen.

The splitting of the C3 protein is the common step to both pathways. In the alternate pathway, C3 is activated spontaneously and, after reacting with the molecules factor P, factor B, and factor D, splits apart. The larger fragment, C3b, binds to the surface of the pathogen and C3a, the smaller fragment, diffuses outward from the site of activation and attracts phagocytes to the site of infection. Surface-bound C3b then activates the rest of the cascade, with the last five proteins, C5–C9, forming the membrane-attack complex (MAC). The MAC can kill certain pathogens by disrupting their osmotic balance. The MAC is especially effective against a broad range of bacteria. The classical pathway is similar, except the early stages of activation require the presence of antibody bound to antigen, and thus is dependent on the adaptive immune response. The earlier fragments of the cascade also have important functions. Phagocytic cells such as macrophages and neutrophils are attracted to an infection site by chemotactic attraction to smaller complement fragments. Additionally, once they arrive, their receptors for surface-bound C3b opsonize the pathogen for phagocytosis and destruction.

Inflammatory Response

The hallmark of the innate immune response is **inflammation**. Inflammation is something everyone has experienced. Stub a toe, cut a finger, or do any activity that causes tissue damage and inflammation will result, with its four characteristics: heat, redness, pain, and swelling (“loss of function” is sometimes mentioned as a fifth characteristic). It is important to note that inflammation does not have to be initiated by an infection, but can also be caused by tissue injuries. The release of damaged cellular contents into the site of injury is enough to stimulate the response, even in the absence of breaks in physical barriers that would allow pathogens to enter (by hitting your thumb with a hammer, for example). The inflammatory reaction brings in phagocytic cells to the damaged area to clear cellular debris and to set the stage for wound repair ([link]).



This reaction also brings in the cells of the innate immune system, allowing them to get rid of the sources of a possible infection. Inflammation is part of a very basic form of immune response. The process not only brings fluid and cells into the site to destroy the pathogen and remove it and debris from the site, but also helps to isolate the site, limiting the spread of the pathogen. **Acute inflammation** is a short-term inflammatory response to an insult to the body. If the cause of the inflammation is not resolved, however, it can lead to chronic inflammation, which is associated with major tissue destruction and fibrosis. **Chronic inflammation** is ongoing inflammation. It can be caused by foreign bodies, persistent pathogens, and autoimmune diseases such as rheumatoid arthritis.

There are four important parts to the inflammatory response:

- *Tissue Injury.* The released contents of injured cells stimulate the release of **mast cell** granules and their potent inflammatory mediators such as histamine, leukotrienes, and prostaglandins. **Histamine** increases the diameter of local blood vessels (vasodilation), causing an increase in blood flow. Histamine also increases the permeability of local capillaries, causing plasma to leak out and form interstitial fluid. This causes the swelling associated with inflammation. Additionally, injured cells, phagocytes, and basophils are sources of

inflammatory mediators, including prostaglandins and leukotrienes. Leukotrienes attract neutrophils from the blood by chemotaxis and increase vascular permeability. Prostaglandins cause vasodilation by relaxing vascular smooth muscle and are a major cause of the pain associated with inflammation. Nonsteroidal anti-inflammatory drugs such as aspirin and ibuprofen relieve pain by inhibiting prostaglandin production.

- *Vasodilation.* Many inflammatory mediators such as histamine are vasodilators that increase the diameters of local capillaries. This causes increased blood flow and is responsible for the heat and redness of inflamed tissue. It allows greater access of the blood to the site of inflammation.
- *Increased Vascular Permeability.* At the same time, inflammatory mediators increase the permeability of the local vasculature, causing leakage of fluid into the interstitial space, resulting in the swelling, or edema, associated with inflammation.
- *Recruitment of Phagocytes.* Leukotrienes are particularly good at attracting neutrophils from the blood to the site of infection by chemotaxis. Following an early neutrophil infiltrate stimulated by macrophage cytokines, more macrophages are recruited to clean up the debris left over at the site. When local infections are severe, neutrophils are attracted to the sites of infections in large numbers, and as they phagocytose the pathogens and subsequently die, their accumulated cellular remains are visible as pus at the infection site.

Overall, inflammation is valuable for many reasons. Not only are the pathogens killed and debris removed, but the increase in vascular permeability encourages the entry of clotting factors, the first step towards wound repair. Inflammation also facilitates the transport of antigen to lymph nodes by dendritic cells for the development of the adaptive immune response.

Chapter Review

Innate immune responses are critical to the early control of infections. Whereas barrier defenses are the body’s first line of physical defense against pathogens, innate immune responses are the first line of physiological defense. Innate responses occur rapidly, but with less specificity and effectiveness than the adaptive immune response. Innate responses can be caused by a variety of cells, mediators, and antibacterial proteins such as complement. Within the first few days of an infection, another series of antibacterial proteins are induced, each with activities against certain bacteria, including opsonization of certain species. Additionally, interferons are induced that protect cells from viruses in their vicinity. Finally, the innate immune response does not stop when the adaptive immune response is

developed. In fact, both can cooperate and one can influence the other in their responses against pathogens.

Interactive Link Questions

Exercise:

Problem:

Visit this website to learn about phagocyte chemotaxis. Phagocyte chemotaxis is the movement of phagocytes according to the secretion of chemical messengers in the form of interleukins and other chemokines. By what means does a phagocyte destroy a bacterium that it has ingested?

Solution:

The bacterium is digested by the phagocyte’s digestive enzymes (contained in its lysosomes).

Review Questions

Exercise:

Problem: Which of the following signs is *not* characteristic of inflammation?

a. redness
b. pain
c. cold
d. swelling

Solution:

C

Exercise:

Problem:

Which of the following is *not* important in the antiviral innate immune response?

a. interferons
b. natural killer cells
c. complement
d. microphages

Solution:

D

Exercise:

Problem:

Enhanced phagocytosis of a cell by the binding of a specific protein is called ________.

a. endocytosis
b. opsonization
c. anaphylaxis
d. complement activation

Solution:

B

Exercise:

Problem: Which of the following leads to the redness of inflammation?

a. increased vascular permeability
b. anaphylactic shock
c. increased blood flow
d. complement activation

Solution:

C

Critical Thinking Questions

Exercise:

Problem:

Describe the process of inflammation in an area that has been traumatized, but not infected.

Solution:

The cell debris and damaged cells induce macrophages to begin to clean them up. Macrophages release cytokines that attract neutrophils, followed by more macrophages. Other mediators released by mast cells increase blood flow to the area and also vascular permeability, allowing the recruited cells to get from the blood to the site of infection, where they can phagocytose the dead cells and debris, preparing the site for wound repair.

Exercise:

Problem:

Describe two early induced responses and what pathogens they affect.

Solution:

Interferons are produced in virally infected cells and cause them to secrete signals for surrounding cells to make antiviral proteins. C-reactive protein is induced to be made by the liver and will opsonize certain species of bacteria.

Glossary

acute inflammation
: inflammation occurring for a limited time period; rapidly developing

chemokine
: soluble, long-range, cell-to-cell communication molecule

chronic inflammation
: inflammation occurring for long periods of time

complement
: enzymatic cascade of constitutive blood proteins that have antipathogen effects, including the direct killing of bacteria

cytokine
: soluble, short-range, cell-to-cell communication molecule

early induced immune response
: includes antimicrobial proteins stimulated during the first several days of an infection

fas ligand
: molecule expressed on cytotoxic T cells and NK cells that binds to the fas molecule on a target cell and induces it do undergo apoptosis

granzyme
: apoptosis-inducing substance contained in granules of NK cells and cytotoxic T cells

histamine
: vasoactive mediator in granules of mast cells and is the primary cause of allergies and anaphylactic shock

inflammation
: basic innate immune response characterized by heat, redness, pain, and swelling

interferons
: early induced proteins made in virally infected cells that cause nearby cells to make antiviral proteins

macrophage
: ameboid phagocyte found in several tissues throughout the body

mast cell
: cell found in the skin and the lining of body cells that contains cytoplasmic granules with vasoactive mediators such as histamine

monocyte
: precursor to macrophages and dendritic cells seen in the blood

neutrophil
: phagocytic white blood cell recruited from the bloodstream to the site of infection via the bloodstream

opsonization

enhancement of phagocytosis by the binding of antibody or antimicrobial protein

pattern recognition receptor (PRR)
leukocyte receptor that binds to specific cell wall components of different bacterial species

perforin
molecule in NK cell and cytotoxic T cell granules that form pores in the membrane of a target cell

phagocytosis
movement of material from the outside to the inside of the cells via vesicles made from invaginations of the plasma membrane

Homeostasis
By the end of this section, you will be able to:

- Define homeostasis
- Describe the factors affecting homeostasis
- Discuss positive and negative feedback mechanisms used in homeostasis
- Describe thermoregulation of endothermic and ectothermic animals

Animal organs and organ systems constantly adjust to internal and external changes through a process called homeostasis (“steady state”). These changes might be in the level of glucose or calcium in blood or in external temperatures. **Homeostasis** means to maintain dynamic equilibrium in the body. It is dynamic because it is constantly adjusting to the changes that the body’s systems encounter. It is equilibrium because body functions are kept within specific ranges. Even an animal that is apparently inactive is maintaining this homeostatic equilibrium.

Homeostatic Process

The goal of homeostasis is the maintenance of equilibrium around a point or value called a **set point**. While there are normal fluctuations from the set point, the body’s systems will usually attempt to go back to this point. A change in the internal or external environment is called a stimulus and is detected by a receptor; the response of the system is to adjust the deviation parameter toward the set point. For instance, if the body becomes too warm, adjustments are made to cool the animal. If the blood’s glucose rises after a meal, adjustments are made to lower the blood glucose level by getting the nutrient into tissues that need it or to store it for later use.

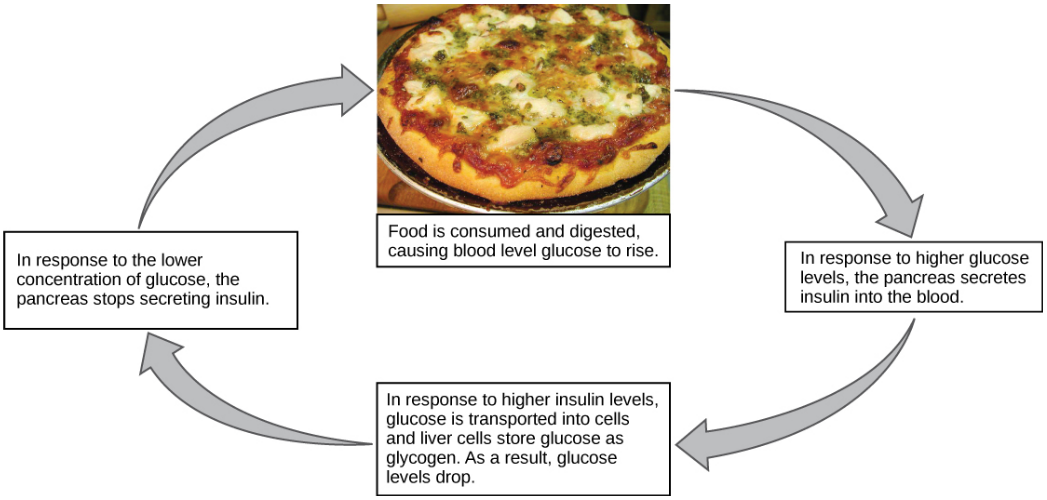
Control of Homeostasis

When a change occurs in an animal’s environment, an adjustment must be made. The receptor senses the change in the environment, then sends a signal to the control center (in most cases, the brain) which in turn generates a response that is signaled to an effector. The effector is a muscle (that contracts or relaxes) or a gland that secretes. Homeostatsis is

maintained by negative feedback loops. Positive feedback loops actually push the organism further out of homeostasis, but may be necessary for life to occur. Homeostasis is controlled by the nervous and endocrine system of mammals.

Negative Feedback Mechanisms

Any homeostatic process that changes the direction of the stimulus is a **negative feedback loop**. It may either increase or decrease the stimulus, but the stimulus is not allowed to continue as it did before the receptor sensed it. In other words, if a level is too high, the body does something to bring it down, and conversely, if a level is too low, the body does something to make it go up. Hence the term negative feedback. An example is animal maintenance of blood glucose levels. When an animal has eaten, blood glucose levels rise. This is sensed by the nervous system. Specialized cells in the pancreas sense this, and the hormone insulin is released by the endocrine system. Insulin causes blood glucose levels to decrease, as would be expected in a negative feedback system, as illustrated in [link]. However, if an animal has not eaten and blood glucose levels decrease, this is sensed in another group of cells in the pancreas, and the hormone glucagon is released causing glucose levels to increase. This is still a negative feedback loop, but not in the direction expected by the use of the term "negative." Another example of an increase as a result of the feedback loop is the control of blood calcium. If calcium levels decrease, specialized cells in the parathyroid gland sense this and release parathyroid hormone (PTH), causing an increased absorption of calcium through the intestines and kidneys and, possibly, the breakdown of bone in order to liberate calcium. The effects of PTH are to raise blood levels of the element. Negative feedback loops are the predominant mechanism used in homeostasis.

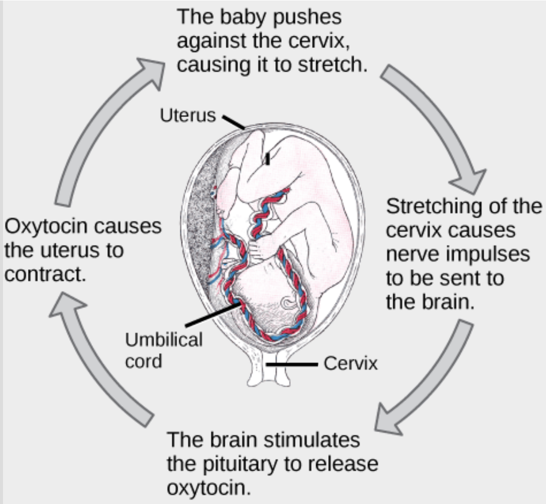


Blood sugar levels are controlled by a negative feedback loop. (credit: modification of work by Jon Sullivan)

Positive Feedback Loop

A **positive feedback loop** maintains the direction of the stimulus, possibly accelerating it. Few examples of positive feedback loops exist in animal bodies, but one is found in the cascade of chemical reactions that result in blood clotting, or coagulation. As one clotting factor is activated, it activates the next factor in sequence until a fibrin clot is achieved. The direction is maintained, not changed, so this is positive feedback. Another example of positive feedback is uterine contractions during childbirth, as illustrated in [link]. The hormone oxytocin, made by the endocrine system, stimulates the contraction of the uterus. This produces pain sensed by the nervous system. Instead of lowering the oxytocin and causing the pain to subside, more oxytocin is produced until the contractions are powerful enough to produce childbirth.

Note:
Art Connection



The birth of a human infant is the result of positive feedback.

State whether each of the following processes is regulated by a positive feedback loop or a negative feedback loop.

a. A person feels satiated after eating a large meal.
b. The blood has plenty of red blood cells. As a result, erythropoietin, a hormone that stimulates the production of new red blood cells, is no longer released from the kidney.

Set Point

It is possible to adjust a system’s set point. When this happens, the feedback loop works to maintain the new setting. An example of this is blood pressure: over time, the normal or set point for blood pressure can increase as a result of continued increases in blood pressure. The body no longer recognizes the elevation as abnormal and no attempt is made to return to the lower set point. The result is the maintenance of an elevated blood pressure that can have harmful effects on the body. Medication can lower blood

pressure and lower the set point in the system to a more healthy level. This is called a process of **alteration** of the set point in a feedback loop.

Changes can be made in a group of body organ systems in order to maintain a set point in another system. This is called **acclimatization**. This occurs, for instance, when an animal migrates to a higher altitude than it is accustomed to. In order to adjust to the lower oxygen levels at the new altitude, the body increases the number of red blood cells circulating in the blood to ensure adequate oxygen delivery to the tissues. Another example of acclimatization is animals that have seasonal changes in their coats: a heavier coat in the winter ensures adequate heat retention, and a light coat in summer assists in keeping body temperature from rising to harmful levels.

Note:
Link to Learning

Feedback mechanisms can be understood in terms of driving a race car along a track: watch a short video lesson on positive and negative feedback loops.
https://www.openstaxcollege.org/l/feedback_loops

Homeostasis: Thermoregulation

Body temperature affects body activities. Generally, as body temperature rises, enzyme activity rises as well. For every ten degree centigrade rise in temperature, enzyme activity doubles, up to a point. Body proteins, including enzymes, begin to denature and lose their function with high heat

(around 50^{o}C for mammals). Enzyme activity will decrease by half for every ten degree centigrade drop in temperature, to the point of freezing, with a few exceptions. Some fish can withstand freezing solid and return to normal with thawing.

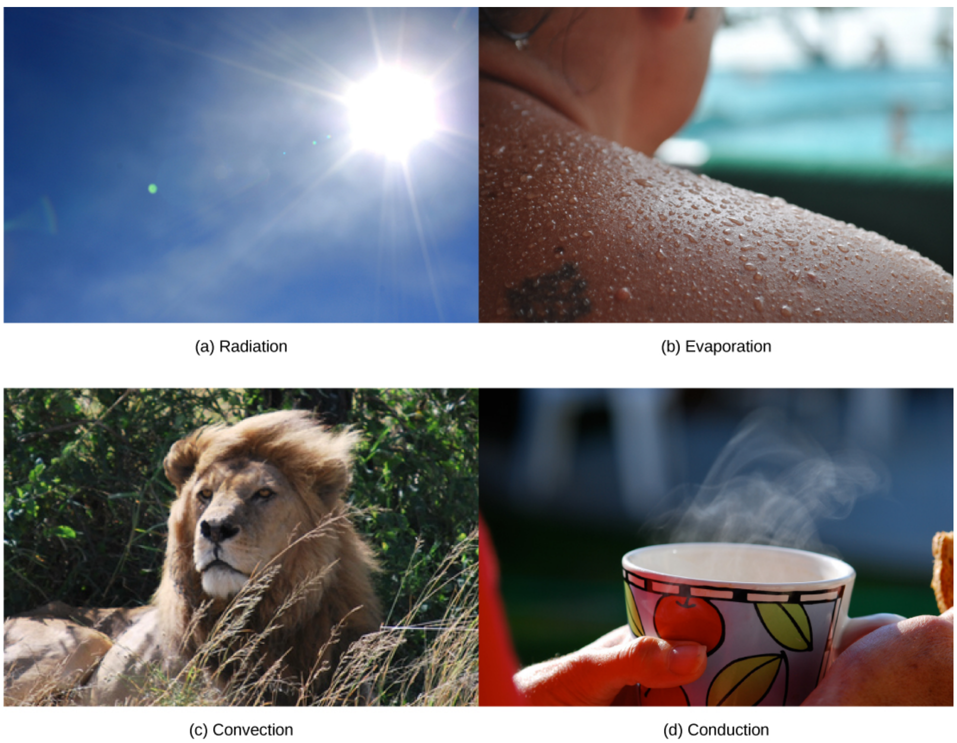
Note:
Link to Learning

Watch this Discovery Channel video on thermoregulation to see illustrations of this process in a variety of animals.
https://www.openstaxcollege.org/l/thermoregulate

Endotherms and Ectotherms

Animals can be divided into two groups: some maintain a constant body temperature in the face of differing environmental temperatures, while others have a body temperature that is the same as their environment and thus varies with the environment. Animals that do not control their body temperature are ectotherms. This group has been called cold-blooded, but the term may not apply to an animal in the desert with a very warm body temperature. In contrast to ectotherms, which rely on external temperatures to set their body temperatures, poikilotherms are animals with constantly varying internal temperatures. An animal that maintains a constant body temperature in the face of environmental changes is called a homeotherm. Endotherms are animals that rely on internal sources for body temperature but which can exhibit extremes in temperature. These animals are able to maintain a level of activity at cooler temperature, which an ectotherm cannot due to differing enzyme levels of activity.

Heat can be exchanged between an animal and its environment through four mechanisms: radiation, evaporation, convection, and conduction ([link]). Radiation is the emission of electromagnetic “heat” waves. Heat comes from the sun in this manner and radiates from dry skin the same way. Heat can be removed with liquid from a surface during evaporation. This occurs when a mammal sweats. Convection currents of air remove heat from the surface of dry skin as the air passes over it. Heat will be conducted from one surface to another during direct contact with the surfaces, such as an animal resting on a warm rock.



Heat can be exchanged by four mechanisms: (a) radiation, (b) evaporation, (c) convection, or (d) conduction. (credit b: modification of work by “Kullez”/Flickr; credit c: modification of work by Chad Rosenthal; credit d: modification of work by “stacey.d”/Flickr)

Heat Conservation and Dissipation

Animals conserve or dissipate heat in a variety of ways. In certain climates, endothermic animals have some form of insulation, such as fur, fat, feathers, or some combination thereof. Animals with thick fur or feathers create an insulating layer of air between their skin and internal organs. Polar bears and seals live and swim in a subfreezing environment and yet maintain a constant, warm, body temperature. The arctic fox, for example, uses its fluffy tail as extra insulation when it curls up to sleep in cold weather. Mammals have a residual effect from shivering and increased muscle activity: arrector pili muscles cause “goose bumps,” causing small hairs to stand up when the individual is cold; this has the intended effect of increasing body temperature. Mammals use layers of fat to achieve the same end. Loss of significant amounts of body fat will compromise an individual’s ability to conserve heat.

Endotherms use their circulatory systems to help maintain body temperature. Vasodilation brings more blood and heat to the body surface, facilitating radiation and evaporative heat loss, which helps to cool the body. Vasoconstriction reduces blood flow in peripheral blood vessels, forcing blood toward the core and the vital organs found there, and conserving heat. Some animals have adaptions to their circulatory system that enable them to transfer heat from arteries to veins, warming blood returning to the heart. This is called a countercurrent heat exchange; it prevents the cold venous blood from cooling the heart and other internal organs. This adaption can be shut down in some animals to prevent overheating the internal organs. The countercurrent adaption is found in many animals, including dolphins, sharks, bony fish, bees, and hummingbirds. In contrast, similar adaptations can help cool endotherms when needed, such as dolphin flukes and elephant ears.

Some ectothermic animals use changes in their behavior to help regulate body temperature. For example, a desert ectothermic animal may simply seek cooler areas during the hottest part of the day in the desert to keep from getting too warm. The same animals may climb onto rocks to capture heat during a cold desert night. Some animals seek water to aid evaporation

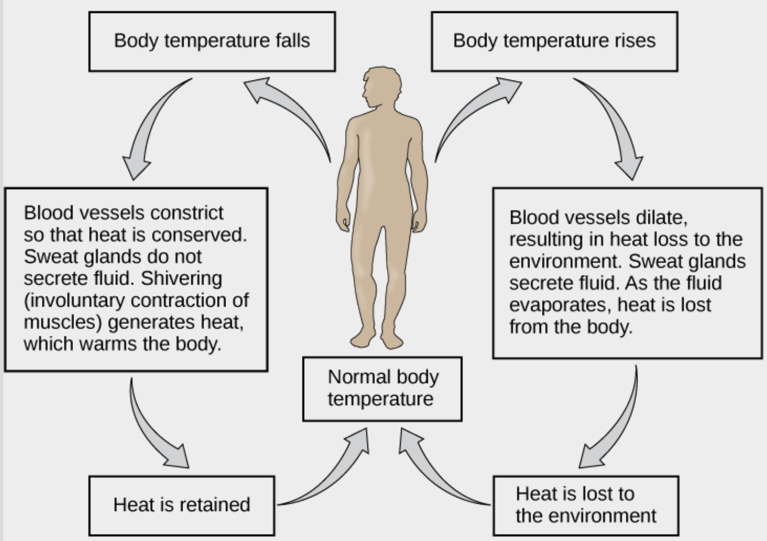
in cooling them, as seen with reptiles. Other ectotherms use group activity such as the activity of bees to warm a hive to survive winter.

Many animals, especially mammals, use metabolic waste heat as a heat source. When muscles are contracted, most of the energy from the ATP used in muscle actions is wasted energy that translates into heat. Severe cold elicits a shivering reflex that generates heat for the body. Many species also have a type of adipose tissue called brown fat that specializes in generating heat.

Neural Control of Thermoregulation

The nervous system is important to **thermoregulation**, as illustrated in [link]. The processes of homeostasis and temperature control are centered in the hypothalamus of the advanced animal brain.

Note:
Art Connection



The body is able to regulate temperature in response to signals from the nervous system.

When bacteria are destroyed by leuckocytes, pyrogens are released into the blood. Pyrogens reset the body’s thermostat to a higher temperature, resulting in fever. How might pyrogens cause the body temperature to rise?

The hypothalamus maintains the set point for body temperature through reflexes that cause vasodilation and sweating when the body is too warm, or vasoconstriction and shivering when the body is too cold. It responds to chemicals from the body. When a bacterium is destroyed by phagocytic leukocytes, chemicals called endogenous pyrogens are released into the blood. These pyrogens circulate to the hypothalamus and reset the thermostat. This allows the body’s temperature to increase in what is commonly called a fever. An increase in body temperature causes iron to be conserved, which reduces a nutrient needed by bacteria. An increase in body heat also increases the activity of the animal’s enzymes and protective cells while inhibiting the enzymes and activity of the invading microorganisms. Finally, heat itself may also kill the pathogen. A fever that was once thought to be a complication of an infection is now understood to be a normal defense mechanism.

Section Summary

Homeostasis is a dynamic equilibrium that is maintained in body tissues and organs. It is dynamic because it is constantly adjusting to the changes that the systems encounter. It is in equilibrium because body functions are kept within a normal range, with some fluctuations around a set point for the processes.

Art Connections

Exercise:

Problem:

[link] State whether each of the following processes are regulated by a positive feedback loop or a negative feedback loop.

a. A person feels satiated after eating a large meal.
b. The blood has plenty of red blood cells. As a result, erythropoietin, a hormone that stimulates the production of new red blood cells, is no longer released from the kidney.

Solution:

[link] Both processes are the result of negative feedback loops. Negative feedback loops, which tend to keep a system at equilibrium, are more common than positive feedback loops.

Exercise:

Problem:

[link] When bacteria are destroyed by leuckocytes, pyrogens are released into the blood. Pyrogens reset the body's thermostat to a higher temperature, resulting in fever. How might pyrogens cause the body temperature to rise?

Solution:

[link] Pyrogens increase body temperature by causing the blood vessels to constrict, inducing shivering, and stopping sweat glands from secreting fluid.

Review Questions

Exercise:

Problem:

When faced with a sudden drop in environmental temperature, an endothermic animal will:

a. experience a drop in its body temperature
b. wait to see if it goes lower
c. increase muscle activity to generate heat

d. add fur or fat to increase insulation

Solution:

C

Exercise:

Problem: Which is an example of negative feedback?

a. lowering of blood glucose after a meal
b. blood clotting after an injury
c. lactation during nursing
d. uterine contractions during labor

Solution:

A

Exercise:

Problem:

Which method of heat exchange occurs during direct contact between the source and animal?

a. radiation
b. evaporation
c. convection
d. conduction

Solution:

D

Exercise:

Problem: The body's thermostat is located in the ________.

a. homeostatic receptor
b. hypothalamus
c. medulla
d. vasodilation center

Solution:

B

Free Response

Exercise:

Problem:

Why are negative feedback loops used to control body homeostasis?

Solution:

An adjustment to a change in the internal or external environment requires a change in the direction of the stimulus. A negative feedback loop accomplishes this, while a positive feedback loop would continue the stimulus and result in harm to the animal.

Exercise:

Problem: Why is a fever a "good thing" during a bacterial infection?

Solution:

Mammalian enzymes increase activity to the point of denaturation, increasing the chemical activity of the cells involved. Bacterial enzymes have a specific temperature for their most efficient activity and are inhibited at either higher or lower temperatures. Fever results

in an increase in the destruction of the invading bacteria by increasing the effectiveness of body defenses and an inhibiting bacterial metabolism.

Exercise:

Problem:

How is a condition such as diabetes a good example of the failure of a set point in humans?

Solution:

Diabetes is often associated with a lack in production of insulin. Without insulin, blood glucose levels go up after a meal, but never go back down to normal levels.

Glossary

acclimatization
: alteration in a body system in response to environmental change

alteration
: change of the set point in a homeostatic system

homeostasis
: dynamic equilibrium maintaining appropriate body functions

negative feedback loop
: feedback to a control mechanism that increases or decreases a stimulus instead of maintaining it

positive feedback loop
: feedback to a control mechanism that continues the direction of a stimulus

set point
: midpoint or target point in homeostasis

thermoregulation

regulation of body temperature

Energy and Heat Balance

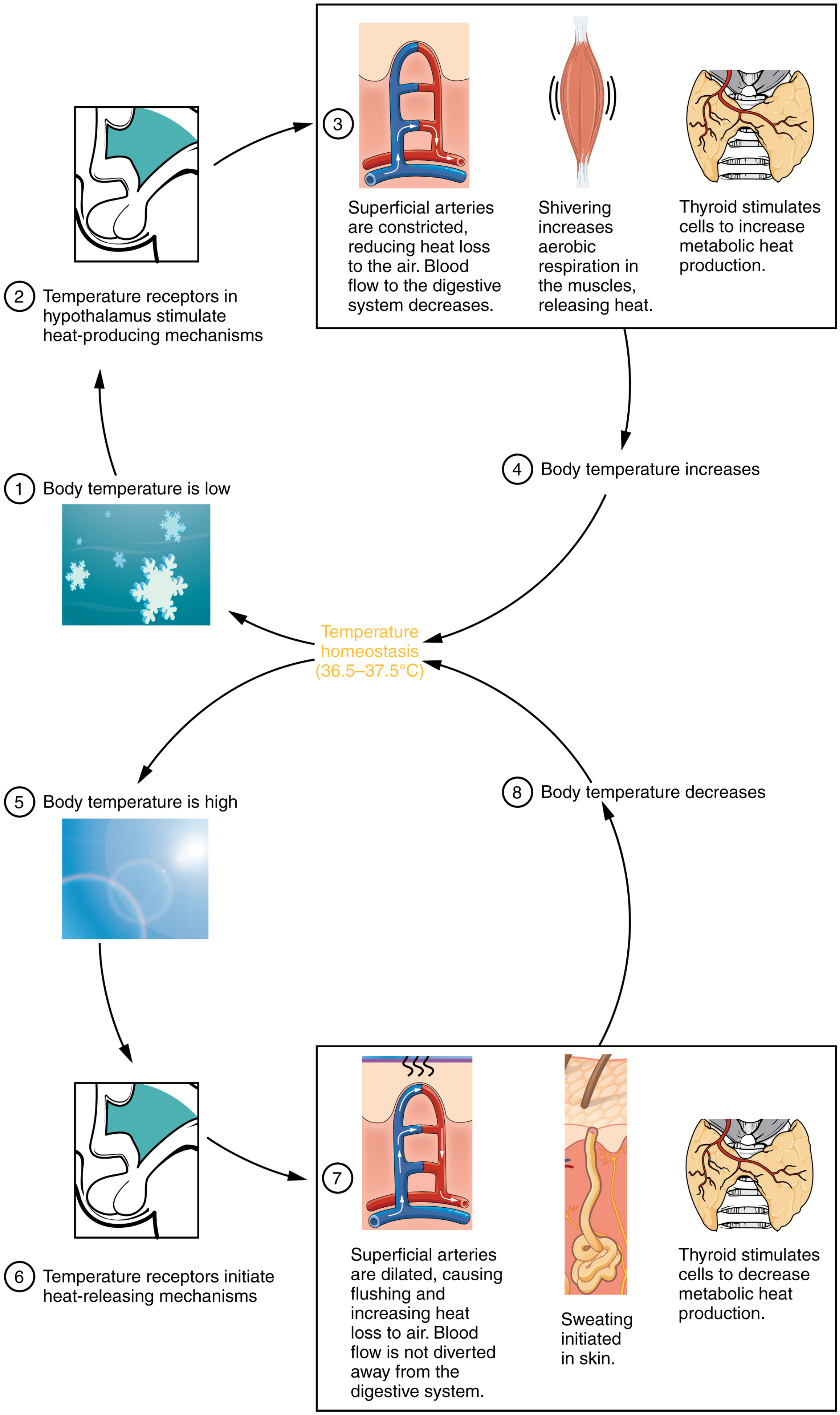
By the end of this section, you will be able to:

- Describe how the body regulates temperature
- Explain the significance of the metabolic rate

The body tightly regulates the body temperature through a process called **thermoregulation**, in which the body can maintain its temperature within certain boundaries, even when the surrounding temperature is very different. The core temperature of the body remains steady at around 36.5–37.5 °C (or 97.7–99.5 °F). In the process of ATP production by cells throughout the body, approximately 60 percent of the energy produced is in the form of heat used to maintain body temperature. Thermoregulation is an example of negative feedback.

The hypothalamus in the brain is the master switch that works as a thermostat to regulate the body's core temperature ([link]). If the temperature is too high, the hypothalamus can initiate several processes to lower it. These include increasing the circulation of the blood to the surface of the body to allow for the dissipation of heat through the skin and initiation of sweating to allow evaporation of water on the skin to cool its surface. Conversely, if the temperature falls below the set core temperature, the hypothalamus can initiate shivering to generate heat. The body uses more energy and generates more heat. In addition, thyroid hormone will stimulate more energy use and heat production by cells throughout the body. An environment is said to be **thermoneutral** when the body does not expend or release energy to maintain its core temperature. For a naked human, this is an ambient air temperature of around 84 °F. If the temperature is higher, for example, when wearing clothes, the body compensates with cooling mechanisms. The body loses heat through the mechanisms of heat exchange.

Hypothalamus Controls Thermoregulation



1 Body temperature is low
2 Temperature receptors in hypothalamus stimulate heat-producing mechanisms
3
Superficial arteries are constricted, reducing heat loss to the air. Blood flow to the digestive system decreases.
Shivering increases aerobic respiration in the muscles, releasing heat.
Thyroid stimulates cells to increase metabolic heat production.
4 Body temperature increases
Temperature homeostasis (36.5–37.5°C)
5 Body temperature is high
6 Temperature receptors initiate heat-releasing mechanisms
7
Superficial arteries are dilated, causing flushing and increasing heat loss to air. Blood flow is not diverted away from the digestive system.
Sweating initiated in skin.
Thyroid stimulates cells to decrease metabolic heat production.
8 Body temperature decreases

The hypothalamus controls thermoregulation.

Mechanisms of Heat Exchange

When the environment is not thermoneutral, the body uses four mechanisms of heat exchange to maintain homeostasis: conduction, convection, radiation, and evaporation. Each of these mechanisms relies on the property of heat to flow from a higher concentration to a lower concentration; therefore, each of the mechanisms of heat exchange varies in rate according to the temperature and conditions of the environment.

Conduction is the transfer of heat by two objects that are in direct contact with one another. It occurs when the skin comes in contact with a cold or warm object. For example, when holding a glass of ice water, the heat from your skin will warm the glass and in turn melt the ice. Alternatively, on a cold day, you might warm up by wrapping your cold hands around a hot mug of coffee. Only about 3 percent of the body's heat is lost through conduction.

Convection is the transfer of heat to the air surrounding the skin. The warmed air rises away from the body and is replaced by cooler air that is subsequently heated. Convection can also occur in water. When the water temperature is lower than the body's temperature, the body loses heat by warming the water closest to the skin, which moves away to be replaced by cooler water. The convection currents created by the temperature changes continue to draw heat away from the body more quickly than the body can replace it, resulting in hyperthermia. About 15 percent of the body's heat is lost through convection.

Radiation is the transfer of heat via infrared waves. This occurs between any two objects when their temperatures differ. A radiator can warm a room via radiant heat. On a sunny day, the radiation from the sun warms the skin. The same principle works from the body to the environment. About 60 percent of the heat lost by the body is lost through radiation.

Evaporation is the transfer of heat by the evaporation of water. Because it takes a great deal of energy for a water molecule to change from a liquid to a gas, evaporating water (in the form of sweat) takes with it a great deal of energy from the skin. However, the rate at which evaporation occurs depends on relative humidity—more sweat evaporates in lower humidity environments. Sweating is the primary means of cooling the body during exercise, whereas at rest, about 20 percent of the heat lost by the body occurs through evaporation.

Metabolic Rate

The **metabolic rate** is the amount of energy consumed minus the amount of energy expended by the body. The **basal metabolic rate (BMR)** describes the amount of daily energy expended by humans at rest, in a neutrally temperate environment, while in the postabsorptive state. It measures how much energy the body needs for normal, basic, daily activity. About 70 percent of all daily energy expenditure comes from the basic functions of the organs in the body. Another 20 percent comes from physical activity, and the remaining 10 percent is necessary for body thermoregulation or temperature control. This rate will be higher if a person is more active or has more lean body mass. As you age, the BMR generally decreases as the percentage of less lean muscle mass decreases.

Chapter Review

Some of the energy from the food that is ingested is used to maintain the core temperature of the body. Most of the energy derived from the food is released as heat. The core temperature is kept around 36.5–37.5 °C (97.7–99.5 °F). This is tightly regulated by the hypothalamus in the brain, which senses changes in the core temperature and operates like a thermostat to increase sweating or shivering, or inducing other mechanisms to return the temperature to its normal range. The body can also gain or lose heat through mechanisms of heat exchange. Conduction transfers heat from one object to another through physical contact. Convection transfers heat to air or water. Radiation transfers heat via infrared radiation. Evaporation transfers heat as water changes state from a liquid to a gas.

Review Questions

Exercise:

Problem:

The body’s temperature is controlled by the _________. This temperature is always kept between _________.

a. pituitary; 36.5–37.5 °C
b. hypothalamus; 97.7–99.5 °F
c. hypothalamus; 36.5–37.5 °F
d. pituitary; 97.7–99.5 °F

Solution:

B

Exercise:

Problem:

Fever increases the body temperature and can induce chills to help cool the temperature back down. What other mechanisms are in place to regulate the body temperature?

a. shivering
b. sweating
c. erection of the hairs on the arms and legs
d. all of the above

Solution:

D

Exercise:

Problem:

The heat you feel on your chair when you stand up was transferred from your skin via _________.

a. conduction
b. convection
c. radiation
d. evaporation

Solution:

A

Exercise:

Problem:

A crowded room warms up through the mechanism of _________.

a. conduction
b. convection
c. radiation
d. evaporation

Solution:

C

Critical Thinking Questions

Exercise:

Problem:

How does vasoconstriction help increase the core temperature of the body?

Solution:

When blood flows to the outer layers of the skin or to the extremities, heat is lost to the environment by the mechanisms of conduction, convection, or radiation. This will cool the blood and the body. Vasoconstriction helps increase the core body temperature by preventing the flow of blood to the outer layer of the skin and outer parts of the extremities.

Exercise:

Problem:

How can the ingestion of food increase the body temperature?

Solution:

The ingestion of food stimulates digestion and processing of the carbohydrates, proteins, and fats. This breakdown of food triggers glycolysis, the Krebs cycle, the electron transport chain, fatty acid oxidation, lipogenesis, and amino acid oxidation to produce energy. Heat is a byproduct of those reactions.

Glossary

basal metabolic rate (BMR)
: amount of energy expended by the body at rest

conduction
: transfer of heat through physical contact

convection
: transfer of heat between the skin and air or water

evaporation
: transfer of heat that occurs when water changes from a liquid to a gas

metabolic rate

amount of energy consumed minus the amount of energy expended by the body

radiation
: transfer of heat via infrared waves

thermoneutral
: external temperature at which the body does not expend any energy for thermoregulation, about 84 °F

thermoregulation
: process of regulating the temperature of the body

Systems of Gas Exchange

By the end of this section, you will be able to:

- Describe the passage of air from the outside environment to the lungs
- Explain how the lungs are protected from particulate matter

The primary function of the respiratory system is to deliver oxygen to the cells of the body’s tissues and remove carbon dioxide, a cell waste product. The main structures of the human respiratory system are the nasal cavity, the trachea, and lungs.

All aerobic organisms require oxygen to carry out their metabolic functions. Along the evolutionary tree, different organisms have devised different means of obtaining oxygen from the surrounding atmosphere. The environment in which the animal lives greatly determines how an animal respires. The complexity of the respiratory system is correlated with the size of the organism. As animal size increases, diffusion distances increase and the ratio of surface area to volume drops. In unicellular organisms, diffusion across the cell membrane is sufficient for supplying oxygen to the cell ([link]). Diffusion is a slow, passive transport process. In order for diffusion to be a feasible means of providing oxygen to the cell, the rate of oxygen uptake must match the rate of diffusion across the membrane. In other words, if the cell were very large or thick, diffusion would not be able to provide oxygen quickly enough to the inside of the cell. Therefore, dependence on diffusion as a means of obtaining oxygen and removing carbon dioxide remains feasible only for small organisms or those with highly-flattened bodies, such as many flatworms (Platyhelminthes). Larger organisms had to evolve specialized respiratory tissues, such as gills, lungs, and respiratory passages accompanied by complex circulatory systems, to transport oxygen throughout their entire body.

The cell of the unicellular algae *Ventricaria ventricosa* is one of the largest known, reaching one to five centimeters in diameter. Like all single-celled organisms, *V. ventricosa* exchanges gases across the cell membrane.

Direct Diffusion

For small multicellular organisms, diffusion across the outer membrane is sufficient to meet their oxygen needs. Gas exchange by direct diffusion across surface membranes is efficient for organisms less than 1 mm in diameter. In simple organisms, such as cnidarians and flatworms, every cell in the body is close to the external environment. Their cells are kept moist and gases diffuse quickly via direct diffusion. Flatworms are small, literally flat worms, which ‘breathe’ through diffusion across the outer membrane ([link]). The flat shape of these organisms increases the surface area for diffusion, ensuring that each cell within the body is close to the outer membrane surface and has access to oxygen. If the flatworm had a

cylindrical body, then the cells in the center would not be able to get oxygen.

This flatworm's process of respiration works by diffusion across the outer membrane. (credit: Stephen Childs)

Skin and Gills

Earthworms and amphibians use their skin (integument) as a respiratory organ. A dense network of capillaries lies just below the skin and facilitates gas exchange between the external environment and the circulatory system. The respiratory surface must be kept moist in order for the gases to dissolve and diffuse across cell membranes.

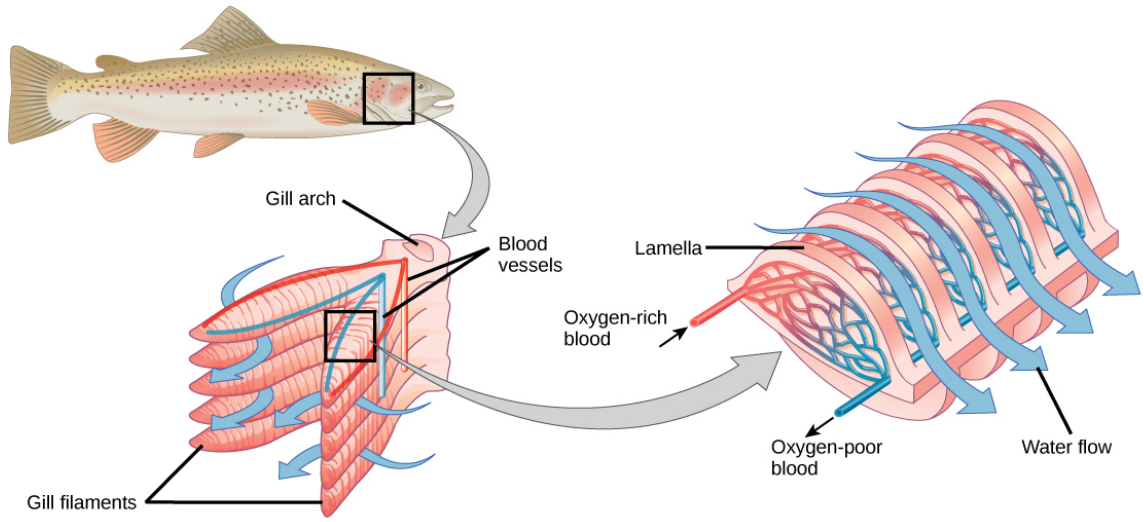
Organisms that live in water need to obtain oxygen from the water. Oxygen dissolves in water but at a lower concentration than in the atmosphere. The atmosphere has roughly 21 percent oxygen. In water, the oxygen concentration is much smaller than that. Fish and many other aquatic organisms have evolved gills to take up the dissolved oxygen from water ([link]). Gills are thin tissue filaments that are highly branched and folded. When water passes over the gills, the dissolved oxygen in water rapidly

diffuses across the gills into the bloodstream. The circulatory system can then carry the oxygenated blood to the other parts of the body. In animals that contain coelomic fluid instead of blood, oxygen diffuses across the gill surfaces into the coelomic fluid. Gills are found in mollusks, annelids, and crustaceans.

This common carp, like many other aquatic organisms, has gills that allow it to obtain oxygen from water. (credit: "Guitardude012"/Wikimedia Commons)

The folded surfaces of the gills provide a large surface area to ensure that the fish gets sufficient oxygen. Diffusion is a process in which material travels from regions of high concentration to low concentration until equilibrium is reached. In this case, blood with a low concentration of oxygen molecules circulates through the gills. The concentration of oxygen molecules in water is higher than the concentration of oxygen molecules in gills. As a result, oxygen molecules diffuse from water (high concentration) to blood (low concentration), as shown in [link]. Similarly, carbon dioxide

molecules in the blood diffuse from the blood (high concentration) to water (low concentration).



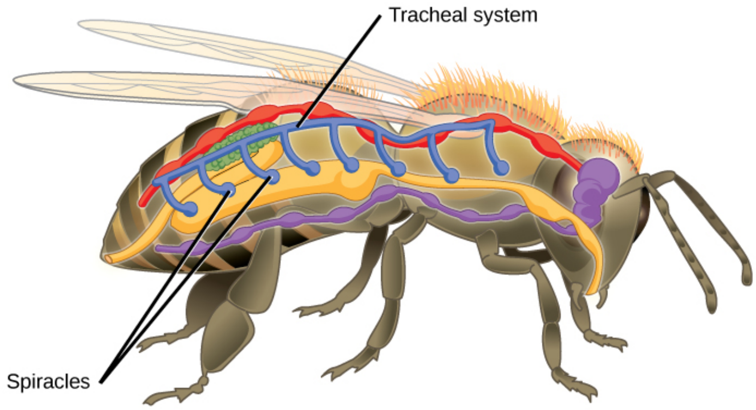
As water flows over the gills, oxygen is transferred to blood via the veins. (credit "fish": modification of work by Duane Raver, NOAA)

Tracheal Systems

Insect respiration is independent of its circulatory system; therefore, the blood does not play a direct role in oxygen transport. Insects have a highly specialized type of respiratory system called the tracheal system, which consists of a network of small tubes that carries oxygen to the entire body. The tracheal system is the most direct and efficient respiratory system in active animals. The tubes in the tracheal system are made of a polymeric material called chitin.

Insect bodies have openings, called spiracles, along the thorax and abdomen. These openings connect to the tubular network, allowing oxygen to pass into the body ([link]) and regulating the diffusion of CO_2 and water

vapor. Air enters and leaves the tracheal system through the spiracles. Some insects can ventilate the tracheal system with body movements.

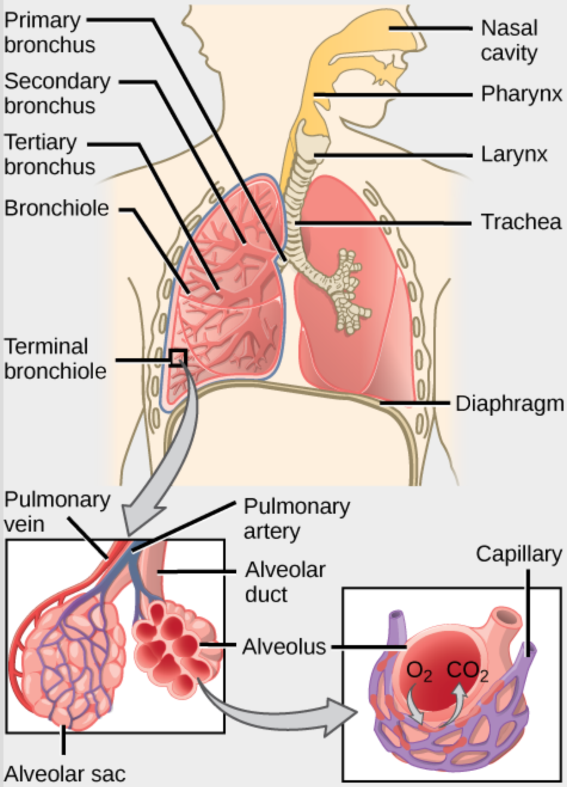


Insects perform respiration via a tracheal system.

Mammalian Systems

In mammals, pulmonary ventilation occurs via inhalation (breathing). During inhalation, air enters the body through the **nasal cavity** located just inside the nose ([link]). As air passes through the nasal cavity, the air is warmed to body temperature and humidified. The respiratory tract is coated with mucus to seal the tissues from direct contact with air. Mucus is high in water. As air crosses these surfaces of the mucous membranes, it picks up water. These processes help equilibrate the air to the body conditions, reducing any damage that cold, dry air can cause. Particulate matter that is floating in the air is removed in the nasal passages via mucus and cilia. The processes of warming, humidifying, and removing particles are important protective mechanisms that prevent damage to the trachea and lungs. Thus, inhalation serves several purposes in addition to bringing oxygen into the respiratory system.

Note:
Art Connection

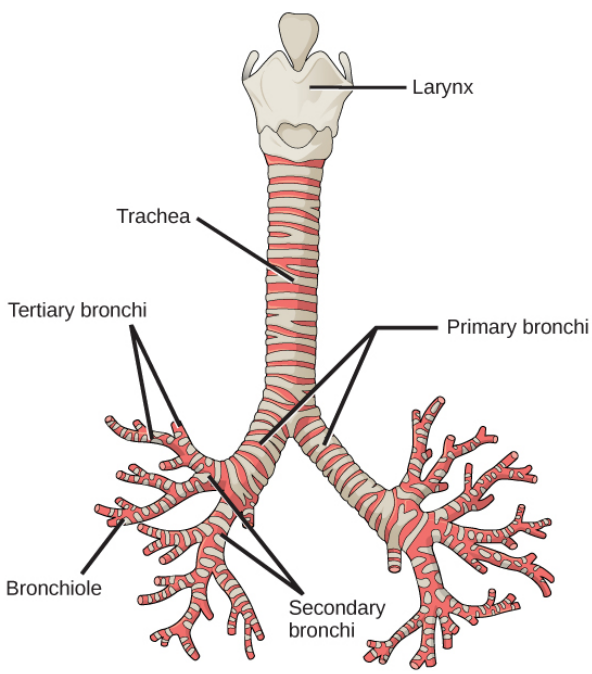


Air enters the respiratory system through the nasal cavity and pharynx, and then passes through the trachea and into the bronchi, which bring air into the lungs. (credit: modification of work by NCI)

Which of the following statements about the mammalian respiratory system is false?

a. When we breathe in, air travels from the pharynx to the trachea.
b. The bronchioles branch into bronchi.
c. Alveolar ducts connect to alveolar sacs.
d. Gas exchange between the lung and blood takes place in the alveolus.

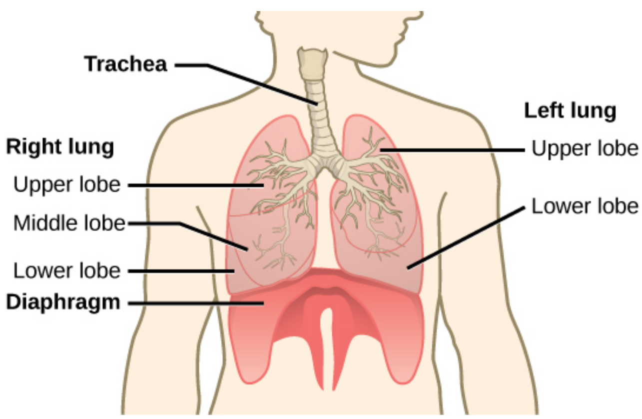
From the nasal cavity, air passes through the **pharynx** (throat) and the **larynx** (voice box), as it makes its way to the **trachea** ([link]). The main function of the trachea is to funnel the inhaled air to the lungs and the exhaled air back out of the body. The human trachea is a cylinder about 10 to 12 cm long and 2 cm in diameter that sits in front of the esophagus and extends from the larynx into the chest cavity where it divides into the two primary bronchi at the midthorax. It is made of incomplete rings of hyaline cartilage and smooth muscle ([link]). The trachea is lined with mucus-producing goblet cells and ciliated epithelia. The cilia propel foreign particles trapped in the mucus toward the pharynx. The cartilage provides strength and support to the trachea to keep the passage open. The smooth muscle can contract, decreasing the trachea's diameter, which causes expired air to rush upwards from the lungs at a great force. The forced exhalation helps expel mucus when we cough. Smooth muscle can contract or relax, depending on stimuli from the external environment or the body's nervous system.



The trachea and bronchi are made of incomplete rings of cartilage. (credit: modification of work by Gray's Anatomy)

Lungs: Bronchi and Alveoli

The end of the trachea bifurcates (divides) to the right and left lungs. The lungs are not identical. The right lung is larger and contains three lobes, whereas the smaller left lung contains two lobes ([link]). The muscular **diaphragm**, which facilitates breathing, is inferior to (below) the lungs and marks the end of the thoracic cavity.

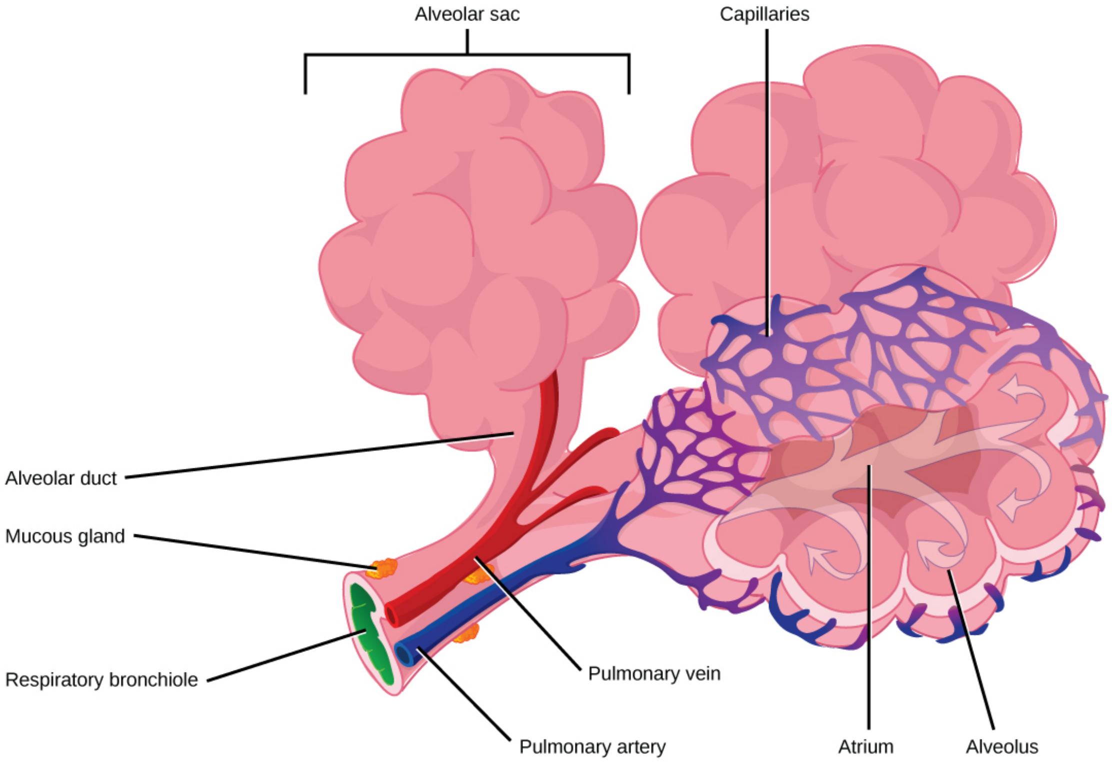


The trachea bifurcates into the right and left bronchi in the lungs. The right lung is made of three lobes and is larger. To accommodate the heart, the left lung is smaller and has only two lobes.

In the lungs, air is diverted into smaller and smaller passages, or **bronchi**. Air enters the lungs through the two **primary (main) bronchi** (singular: bronchus). Each bronchus divides into secondary bronchi, then into tertiary bronchi, which in turn divide, creating smaller and smaller diameter **bronchioles** as they split and spread through the lung. Like the trachea, the bronchi are made of cartilage and smooth muscle. At the bronchioles, the cartilage is replaced with elastic fibers. Bronchi are innervated by nerves of both the parasympathetic and sympathetic nervous systems that control muscle contraction (parasympathetic) or relaxation (sympathetic) in the bronchi and bronchioles, depending on the nervous system's cues. In humans, bronchioles with a diameter smaller than 0.5 mm are the **respiratory bronchioles**. They lack cartilage and therefore rely on inhaled air to support their shape. As the passageways decrease in diameter, the relative amount of smooth muscle increases.

The **terminal bronchioles** subdivide into microscopic branches called respiratory bronchioles. The respiratory bronchioles subdivide into several alveolar ducts. Numerous alveoli and alveolar sacs surround the alveolar ducts. The alveolar sacs resemble bunches of grapes tethered to the end of the bronchioles ([link]). In the acinar region, the **alveolar ducts** are attached to the end of each bronchiole. At the end of each duct are approximately 100 **alveolar sacs**, each containing 20 to 30 **alveoli** that are 200 to 300 microns in diameter. Gas exchange occurs only in alveoli. Alveoli are made of thin-walled parenchymal cells, typically one-cell thick, that look like tiny bubbles within the sacs. Alveoli are in direct contact with capillaries (one-cell thick) of the circulatory system. Such intimate contact ensures that oxygen will diffuse from alveoli into the blood and be distributed to the cells of the body. In addition, the carbon dioxide that was produced by cells as a waste product will diffuse from the blood into alveoli to be exhaled. The anatomical arrangement of capillaries and alveoli emphasizes the structural and functional relationship of the respiratory and circulatory systems. Because there are so many alveoli (~300 million per lung) within each alveolar sac and so many sacs at the end of each alveolar duct, the lungs have a sponge-like consistency. This organization produces a very large surface area that is available for gas exchange. The surface area of alveoli in the lungs is approximately 75 m^2. This large surface area,

combined with the thin-walled nature of the alveolar parenchymal cells, allows gases to easily diffuse across the cells.



Terminal bronchioles are connected by respiratory bronchioles to alveolar ducts and alveolar sacs. Each alveolar sac contains 20 to 30 spherical alveoli and has the appearance of a bunch of grapes. Air flows into the atrium of the alveolar sac, then circulates into alveoli where gas exchange occurs with the capillaries. Mucous glands secrete mucous into the airways, keeping them moist and flexible. (credit: modification of work by Mariana Ruiz Villareal)

Note:
Link to Learning

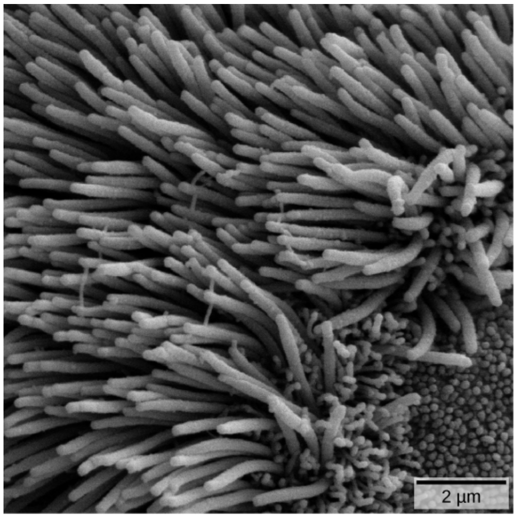
Watch the following video to review the respiratory system. https://www.openstaxcollege.org/l/lungs_pulmonary

Protective Mechanisms

The air that organisms breathe contains **particulate matter** such as dust, dirt, viral particles, and bacteria that can damage the lungs or trigger allergic immune responses. The respiratory system contains several protective mechanisms to avoid problems or tissue damage. In the nasal cavity, hairs and mucus trap small particles, viruses, bacteria, dust, and dirt to prevent their entry.

If particulates do make it beyond the nose, or enter through the mouth, the bronchi and bronchioles of the lungs also contain several protective devices. The lungs produce **mucus**—a sticky substance made of **mucin**, a complex glycoprotein, as well as salts and water—that traps particulates. The bronchi and bronchioles contain cilia, small hair-like projections that line the walls of the bronchi and bronchioles ([link]). These cilia beat in unison and move mucus and particles out of the bronchi and bronchioles back up to the throat where it is swallowed and eliminated via the esophagus.

In humans, for example, tar and other substances in cigarette smoke destroy or paralyze the cilia, making the removal of particles more difficult. In addition, smoking causes the lungs to produce more mucus, which the damaged cilia are not able to move. This causes a persistent cough, as the lungs try to rid themselves of particulate matter, and makes smokers more susceptible to respiratory ailments.



The bronchi and bronchioles contain cilia that help move mucus and other particles out of the lungs. (credit: Louisa Howard, modification of work by Dartmouth Electron Microscope Facility)

Section Summary

Animal respiratory systems are designed to facilitate gas exchange. In mammals, air is warmed and humidified in the nasal cavity. Air then travels down the pharynx, through the trachea, and into the lungs. In the lungs, air passes through the branching bronchi, reaching the respiratory bronchioles, which house the first site of gas exchange. The respiratory bronchioles open into the alveolar ducts, alveolar sacs, and alveoli. Because there are so many alveoli and alveolar sacs in the lung, the surface area for gas exchange is very large. Several protective mechanisms are in place to prevent damage or infection. These include the hair and mucus in the nasal cavity that trap dust, dirt, and other particulate matter before they can enter

the system. In the lungs, particles are trapped in a mucus layer and transported via cilia up to the esophageal opening at the top of the trachea to be swallowed.

Exercise:

Problem:

[link] Which of the following statements about the mammalian respiratory system is false?

a. When we breathe in, air travels from the pharynx to the trachea.
b. The bronchioles branch into bronchi.
c. Alveolar ducts connect to alveolar sacs.
d. Gas exchange between the lung and blood takes place in the alveolus.

Solution:

[link] B

Review Questions

Exercise:

Problem: The respiratory system ________.

a. provides body tissues with oxygen
b. provides body tissues with oxygen and carbon dioxide
c. establishes how many breaths are taken per minute
d. provides the body with carbon dioxide

Solution:

A

Exercise:

Problem:

Air is warmed and humidified in the nasal passages. This helps to ________.

a. ward off infection
b. decrease sensitivity during breathing
c. prevent damage to the lungs
d. all of the above

Solution:

C

Exercise:

Problem: Which is the order of airflow during inhalation?

a. nasal cavity, trachea, larynx, bronchi, bronchioles, alveoli
b. nasal cavity, larynx, trachea, bronchi, bronchioles, alveoli
c. nasal cavity, larynx, trachea, bronchioles, bronchi, alveoli
d. nasal cavity, trachea, larynx, bronchi, bronchioles, alveoli

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Solution:

B

Free Response

Exercise:

Problem:

Describe the function of these terms and describe where they are located: main bronchus, trachea, alveoli, and acinus.

Solution:

The main bronchus is the conduit in the lung that funnels air to the airways where gas exchange occurs. The main bronchus attaches the lungs to the very end of the trachea where it bifurcates. The trachea is the cartilaginous structure that extends from the pharynx to the primary bronchi. It serves to funnel air to the lungs. The alveoli are the sites of gas exchange; they are located at the terminal regions of the lung and are attached to the respiratory bronchioles. The acinus is the structure in the lung where gas exchange occurs.

Exercise:

Problem: How does the structure of alveoli maximize gas exchange?

Solution:

The sac-like structure of the alveoli increases their surface area. In addition, the alveoli are made of thin-walled parenchymal cells. These features allow gases to easily diffuse across the cells.

Glossary

alveolar duct
: duct that extends from the terminal bronchiole to the alveolar sac

alveolar sac
: structure consisting of two or more alveoli that share a common opening

alveolus
: (plural: alveoli) (also, air sac) terminal region of the lung where gas exchange occurs

bronchus
: (plural: bronchi) smaller branch of cartilaginous tissue that stems off of the trachea; air is funneled through the bronchi to the region where gas

exchange occurs in alveoli

bronchiole
: airway that extends from the main tertiary bronchi to the alveolar sac

diaphragm
: domed-shaped skeletal muscle located under lungs that separates the thoracic cavity from the abdominal cavity

larynx
: voice box, a short passageway connecting the pharynx and the trachea

mucin
: complex glycoprotein found in mucus

mucus
: sticky protein-containing fluid secretion in the lung that traps particulate matter to be expelled from the body

nasal cavity
: opening of the respiratory system to the outside environment

particulate matter
: small particle such as dust, dirt, viral particles, and bacteria that are in the air

pharynx
: throat; a tube that starts in the internal nares and runs partway down the neck, where it opens into the esophagus and the larynx

primary bronchus
: (also, main bronchus) region of the airway within the lung that attaches to the trachea and bifurcates to each lung where it branches into secondary bronchi

respiratory bronchiole
: terminal portion of the bronchiole tree that is attached to the terminal bronchioles and alveoli ducts, alveolar sacs, and alveoli

terminal bronchiole
: region of bronchiole that attaches to the respiratory bronchioles

trachea
: cartilaginous tube that transports air from the larynx to the primary bronchi

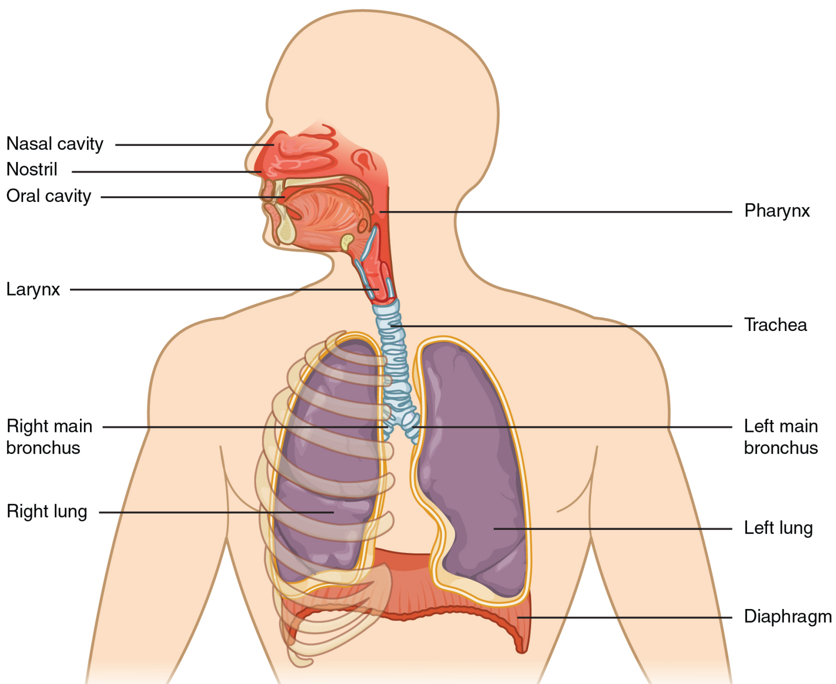
Organs and Structures of the Respiratory System

By the end of this section, you will be able to:

- List the structures that make up the respiratory system
- Describe how the respiratory system processes oxygen and CO_2
- Compare and contrast the functions of upper respiratory tract with the lower respiratory tract

The major organs of the respiratory system function primarily to provide oxygen to body tissues for cellular respiration, remove the waste product carbon dioxide, and help to maintain acid-base balance. Portions of the respiratory system are also used for non-vital functions, such as sensing odors, speech production, and for straining, such as during childbirth or coughing ([link]).

Major Respiratory Structures



The major respiratory structures span the nasal cavity to the diaphragm.

Functionally, the respiratory system can be divided into a conducting zone and a respiratory zone. The **conducting zone** of the respiratory system includes the organs and structures not directly involved in gas exchange. The gas exchange occurs in the **respiratory zone**.

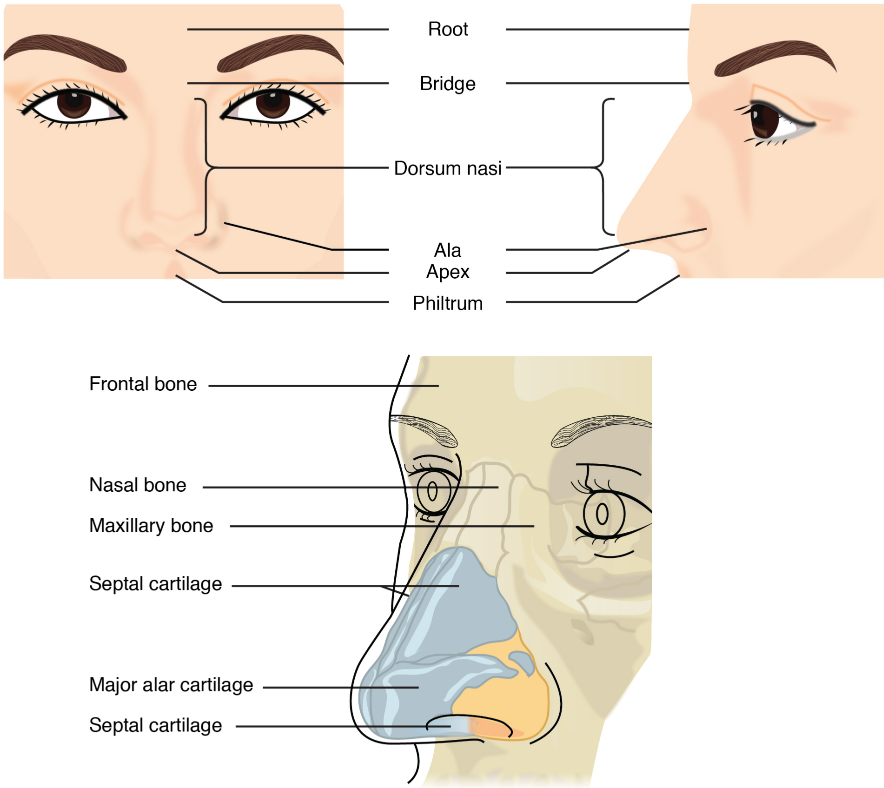
Conducting Zone

The major functions of the conducting zone are to provide a route for incoming and outgoing air, remove debris and pathogens from the incoming air, and warm and humidify the incoming air. Several structures within the conducting zone perform other functions as well. The epithelium of the nasal passages, for example, is essential to sensing odors, and the bronchial epithelium that lines the lungs can metabolize some airborne carcinogens.

The Nose and its Adjacent Structures

The major entrance and exit for the respiratory system is through the nose. When discussing the nose, it is helpful to divide it into two major sections: the external nose, and the nasal cavity or internal nose.

The **external nose** consists of the surface and skeletal structures that result in the outward appearance of the nose and contribute to its numerous functions ([link]). The **root** is the region of the nose located between the eyebrows. The **bridge** is the part of the nose that connects the root to the rest of the nose. The **dorsum nasi** is the length of the nose. The **apex** is the tip of the nose. On either side of the apex, the nostrils are formed by the alae (singular = ala). An **ala** is a cartilaginous structure that forms the lateral side of each **naris** (plural = nares), or nostril opening. The **philtrum** is the concave surface that connects the apex of the nose to the upper lip.
Nose



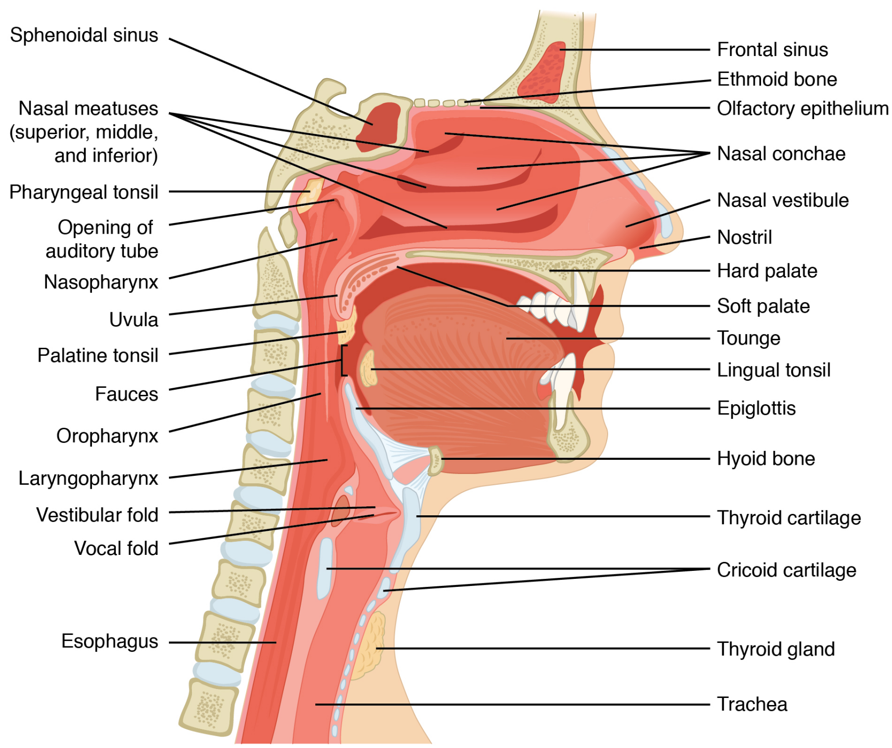
This illustration shows features of the external nose (top) and skeletal features of the nose (bottom).

Underneath the thin skin of the nose are its skeletal features (see [link], lower illustration). While the root and bridge of the nose consist of bone, the protruding portion of the nose is composed of cartilage. As a result, when looking at a skull, the nose is missing. The **nasal bone** is one of a pair of bones that lies under the root and bridge of the nose. The nasal bone articulates superiorly with the frontal bone and laterally with the maxillary bones. Septal cartilage is flexible hyaline cartilage connected to the nasal bone, forming the dorsum nasi. The **alar cartilage** consists of the apex of the nose; it surrounds the naris.

The nares open into the nasal cavity, which is separated into left and right sections by the nasal septum ([link]). The **nasal septum** is formed anteriorly by a portion of the septal cartilage (the flexible portion you can

touch with your fingers) and posteriorly by the perpendicular plate of the ethmoid bone (a cranial bone located just posterior to the nasal bones) and the thin vomer bones (whose name refers to its plough shape). Each lateral wall of the nasal cavity has three bony projections, called the superior, middle, and inferior nasal conchae. The inferior conchae are separate bones, whereas the superior and middle conchae are portions of the ethmoid bone. Conchae serve to increase the surface area of the nasal cavity and to disrupt the flow of air as it enters the nose, causing air to bounce along the epithelium, where it is cleaned and warmed. The conchae and **meatuses** also conserve water and prevent dehydration of the nasal epithelium by trapping water during exhalation. The floor of the nasal cavity is composed of the palate. The hard palate at the anterior region of the nasal cavity is composed of bone. The soft palate at the posterior portion of the nasal cavity consists of muscle tissue. Air exits the nasal cavities via the internal nares and moves into the pharynx.

Upper Airway



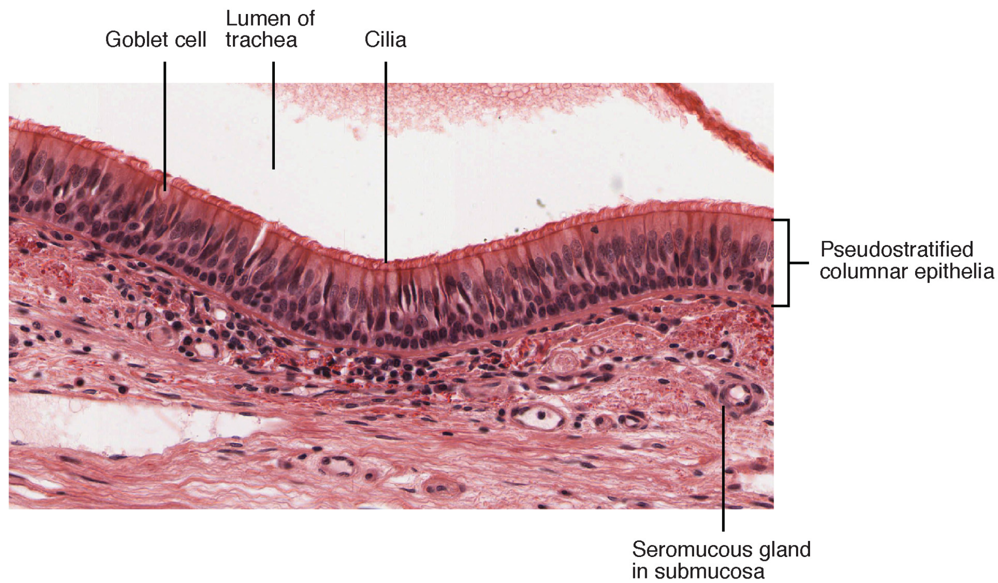
Several bones that help form the walls of the nasal cavity have air-containing spaces called the paranasal sinuses, which serve to warm and humidify incoming air. Sinuses are lined with a mucosa. Each **paranasal sinus** is named for its associated bone: frontal sinus, maxillary sinus,

sphenoidal sinus, and ethmoidal sinus. The sinuses produce mucus and lighten the weight of the skull.

The nares and anterior portion of the nasal cavities are lined with mucous membranes, containing sebaceous glands and hair follicles that serve to prevent the passage of large debris, such as dirt, through the nasal cavity. An olfactory epithelium used to detect odors is found deeper in the nasal cavity.

The conchae, meatuses, and paranasal sinuses are lined by **respiratory epithelium** composed of pseudostratified ciliated columnar epithelium ([link]). The epithelium contains goblet cells, one of the specialized, columnar epithelial cells that produce mucus to trap debris. The cilia of the respiratory epithelium help remove the mucus and debris from the nasal cavity with a constant beating motion, sweeping materials towards the throat to be swallowed. Interestingly, cold air slows the movement of the cilia, resulting in accumulation of mucus that may in turn lead to a runny nose during cold weather. This moist epithelium functions to warm and humidify incoming air. Capillaries located just beneath the nasal epithelium warm the air by convection. Serous and mucus-producing cells also secrete the lysozyme enzyme and proteins called defensins, which have antibacterial properties. Immune cells that patrol the connective tissue deep to the respiratory epithelium provide additional protection.

Pseudostratified Ciliated Columnar Epithelium



Respiratory epithelium is pseudostratified ciliated columnar epithelium. Seromucous glands provide lubricating mucus. LM × 680. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

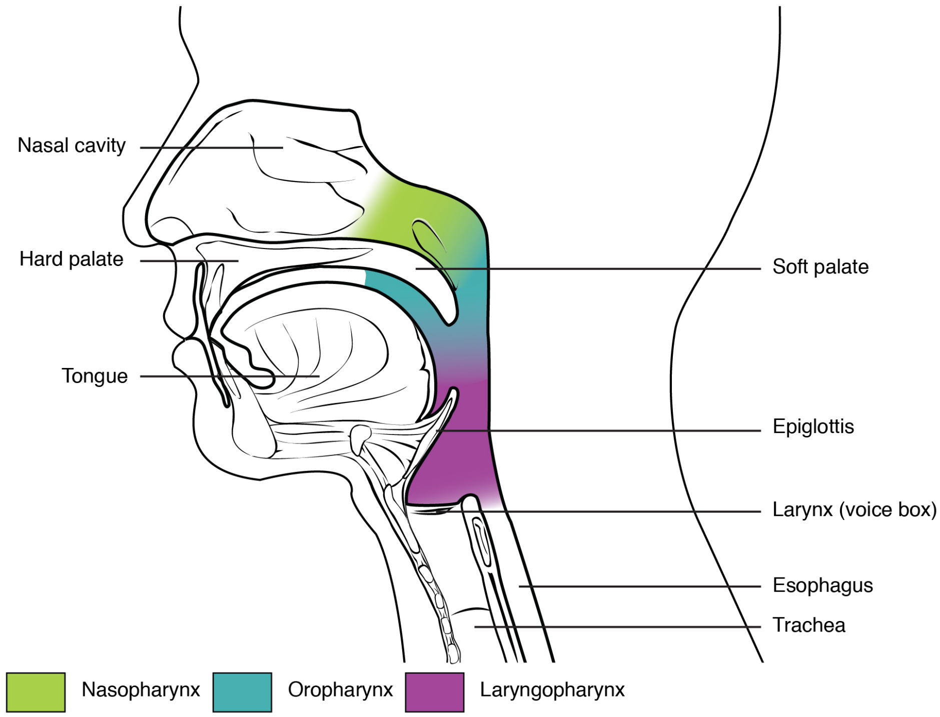
Note:

View the University of Michigan WebScope to explore the tissue sample in greater detail.

Pharynx

The **pharynx** is a tube formed by skeletal muscle and lined by mucous membrane that is continuous with that of the nasal cavities (see [link]). The pharynx is divided into three major regions: the nasopharynx, the oropharynx, and the laryngopharynx ([link]).

Divisions of the Pharynx



The pharynx is divided into three regions: the nasopharynx, the oropharynx, and the laryngopharynx.

The **nasopharynx** is flanked by the conchae of the nasal cavity, and it serves only as an airway. At the top of the nasopharynx are the pharyngeal tonsils. A **pharyngeal tonsil**, also called an adenoid, is an aggregate of lymphoid reticular tissue similar to a lymph node that lies at the superior portion of the nasopharynx. The function of the pharyngeal tonsil is not well understood, but it contains a rich supply of lymphocytes and is covered with ciliated epithelium that traps and destroys invading pathogens that enter during inhalation. The pharyngeal tonsils are large in children, but interestingly, tend to regress with age and may even disappear. The uvula is a small bulbous, teardrop-shaped structure located at the apex of the soft palate. Both the uvula and soft palate move like a pendulum during swallowing, swinging upward to close off the nasopharynx to prevent ingested materials from entering the nasal cavity. In addition, auditory

(Eustachian) tubes that connect to each middle ear cavity open into the nasopharynx. This connection is why colds often lead to ear infections.

The **oropharynx** is a passageway for both air and food. The oropharynx is bordered superiorly by the nasopharynx and anteriorly by the oral cavity. The **fauces** is the opening at the connection between the oral cavity and the oropharynx. As the nasopharynx becomes the oropharynx, the epithelium changes from pseudostratified ciliated columnar epithelium to stratified squamous epithelium. The oropharynx contains two distinct sets of tonsils, the palatine and lingual tonsils. A **palatine tonsil** is one of a pair of structures located laterally in the oropharynx in the area of the fauces. The **lingual tonsil** is located at the base of the tongue. Similar to the pharyngeal tonsil, the palatine and lingual tonsils are composed of lymphoid tissue, and trap and destroy pathogens entering the body through the oral or nasal cavities.

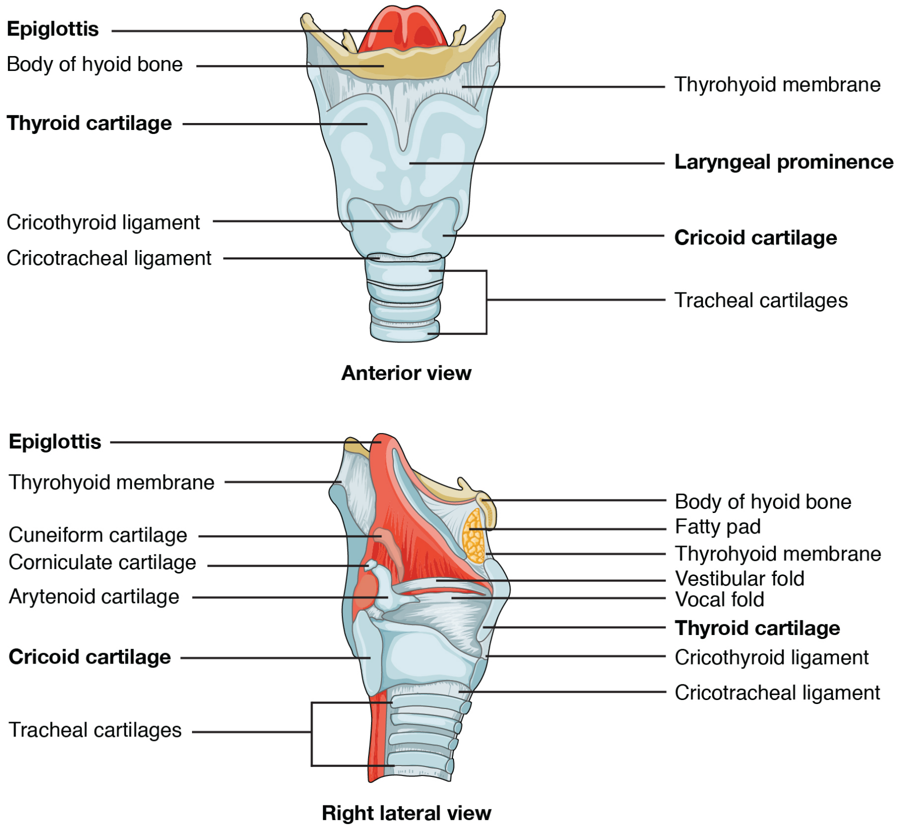
The **laryngopharynx** is inferior to the oropharynx and posterior to the larynx. It continues the route for ingested material and air until its inferior end, where the digestive and respiratory systems diverge. The stratified squamous epithelium of the oropharynx is continuous with the laryngopharynx. Anteriorly, the laryngopharynx opens into the larynx, whereas posteriorly, it enters the esophagus.

Larynx

The **larynx** is a cartilaginous structure inferior to the laryngopharynx that connects the pharynx to the trachea and helps regulate the volume of air that enters and leaves the lungs ([link]). The structure of the larynx is formed by several pieces of cartilage. Three large cartilage pieces—the thyroid cartilage (anterior), epiglottis (superior), and cricoid cartilage (inferior)—form the major structure of the larynx. The **thyroid cartilage** is the largest piece of cartilage that makes up the larynx. The thyroid cartilage consists of the **laryngeal prominence**, or “Adam’s apple,” which tends to be more prominent in males. The thick **cricoid cartilage** forms a ring, with a wide posterior region and a thinner anterior region. Three smaller, paired cartilages—the arytenoids, corniculates, and cuneiforms—attach to the

epiglottis and the vocal cords and muscle that help move the vocal cords to produce speech.

Larynx

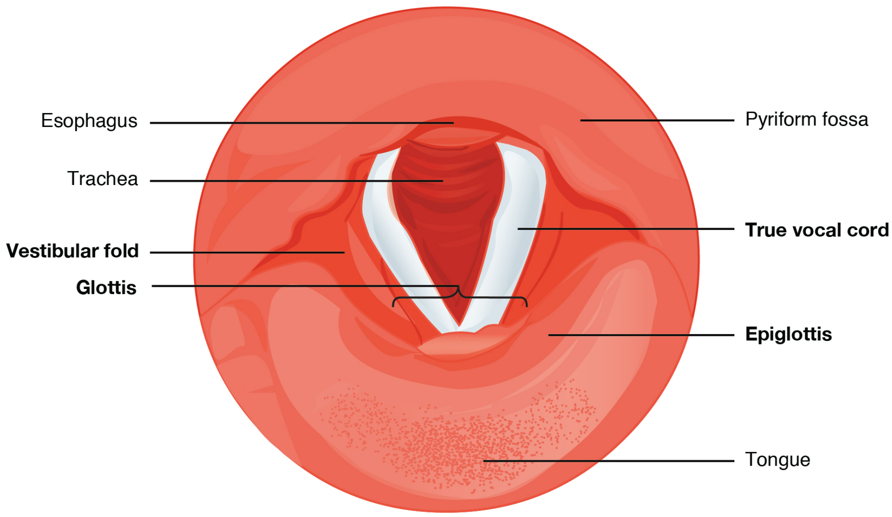


The larynx extends from the laryngopharynx and the hyoid bone to the trachea.

The **epiglottis**, attached to the thyroid cartilage, is a very flexible piece of elastic cartilage that covers the opening of the trachea (see [link]). When in the “closed” position, the unattached end of the epiglottis rests on the glottis. The **glottis** is composed of the vestibular folds, the true vocal cords, and the space between these folds ([link]). A **vestibular fold**, or false vocal cord, is one of a pair of folded sections of mucous membrane. A **true vocal cord** is one of the white, membranous folds attached by muscle to the thyroid and arytenoid cartilages of the larynx on their outer edges. The inner edges of the true vocal cords are free, allowing oscillation to produce sound. The size of the membranous folds of the true vocal cords differs

between individuals, producing voices with different pitch ranges. Folds in males tend to be larger than those in females, which create a deeper voice. The act of swallowing causes the pharynx and larynx to lift upward, allowing the pharynx to expand and the epiglottis of the larynx to swing downward, closing the opening to the trachea. These movements produce a larger area for food to pass through, while preventing food and beverages from entering the trachea.

Vocal Cords



The true vocal cords and vestibular folds of the larynx are viewed inferiorly from the laryngopharynx.

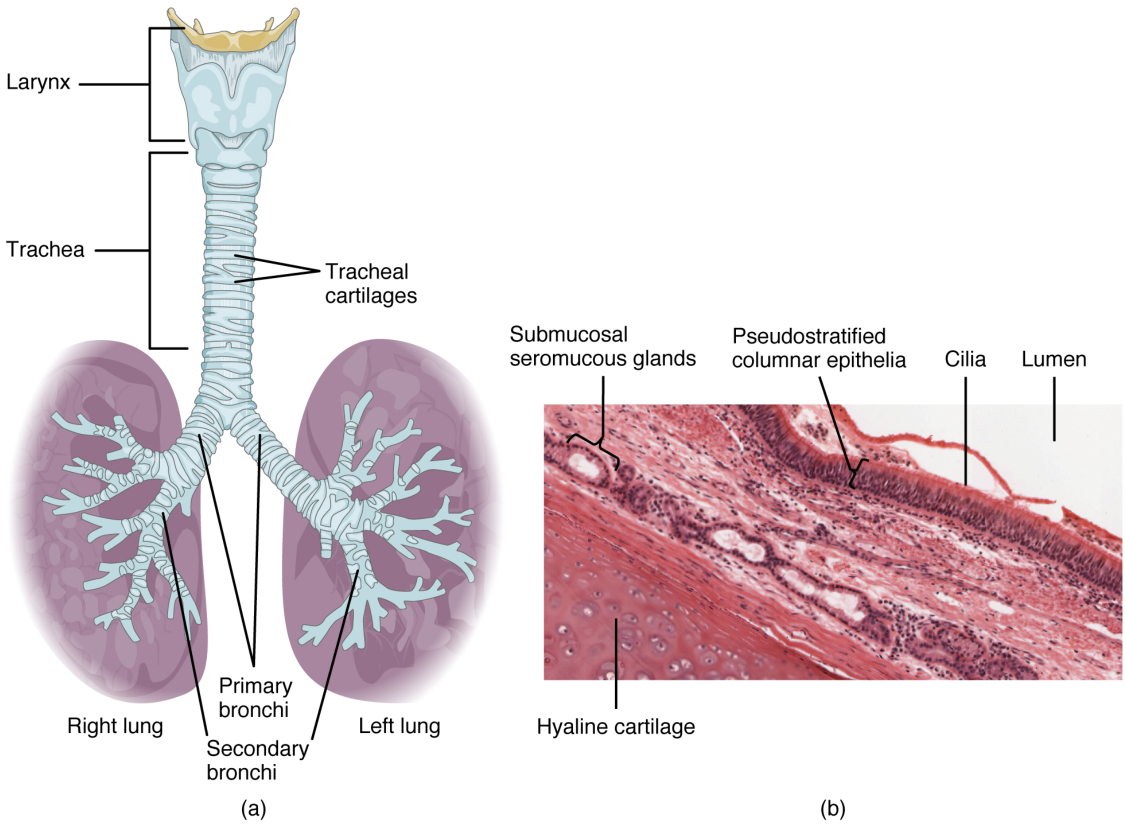
Continuous with the laryngopharynx, the superior portion of the larynx is lined with stratified squamous epithelium, transitioning into pseudostratified ciliated columnar epithelium that contains goblet cells. Similar to the nasal cavity and nasopharynx, this specialized epithelium produces mucus to trap debris and pathogens as they enter the trachea. The cilia beat the mucus upward towards the laryngopharynx, where it can be swallowed down the esophagus.

Trachea

The trachea (windpipe) extends from the larynx toward the lungs ([link]**a**). The **trachea** is formed by 16 to 20 stacked, C-shaped pieces of hyaline cartilage that are connected by dense connective tissue. The **trachealis muscle** and elastic connective tissue together form the **fibroelastic membrane**, a flexible membrane that closes the posterior surface of the trachea, connecting the C-shaped cartilages. The fibroelastic membrane allows the trachea to stretch and expand slightly during inhalation and exhalation, whereas the rings of cartilage provide structural support and prevent the trachea from collapsing. In addition, the trachealis muscle can be contracted to force air through the trachea during exhalation. The trachea is lined with pseudostratified ciliated columnar epithelium, which is continuous with the larynx. The esophagus borders the trachea posteriorly.

Trachea

(a) The tracheal tube is formed by stacked, C-shaped pieces of hyaline cartilage. (b) The layer visible in this cross-section of tracheal wall tissue between the hyaline cartilage and the lumen of the trachea is the mucosa, which is composed of pseudostratified ciliated columnar epithelium that contains goblet cells. LM × 1220. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)



Bronchial Tree

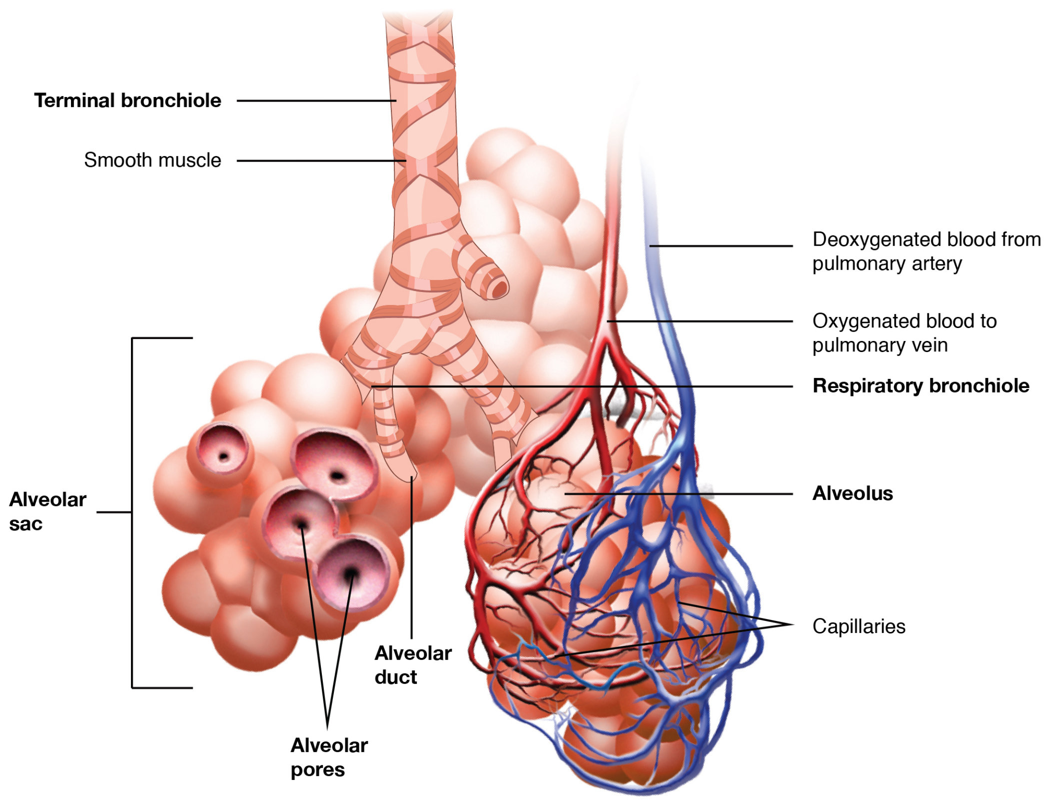
The trachea branches into the right and left primary **bronchi** at the carina. These bronchi are also lined by pseudostratified ciliated columnar epithelium containing mucus-producing goblet cells ([link]**b**). The carina is a raised structure that contains specialized nervous tissue that induces violent coughing if a foreign body, such as food, is present. Rings of cartilage, similar to those of the trachea, support the structure of the bronchi and prevent their collapse. The primary bronchi enter the lungs at the hilum, a concave region where blood vessels, lymphatic vessels, and nerves also enter the lungs. The bronchi continue to branch into bronchial a tree. A **bronchial tree** (or respiratory tree) is the collective term used for these multiple-branched bronchi. The main function of the bronchi, like other conducting zone structures, is to provide a passageway for air to move into and out of each lung. In addition, the mucous membrane traps debris and pathogens.

A **bronchiole** branches from the tertiary bronchi. Bronchioles, which are about 1 mm in diameter, further branch until they become the tiny terminal bronchioles, which lead to the structures of gas exchange. There are more than 1000 terminal bronchioles in each lung. The muscular walls of the bronchioles do not contain cartilage like those of the bronchi. This muscular wall can change the size of the tubing to increase or decrease airflow through the tube.

Respiratory Zone

In contrast to the conducting zone, the respiratory zone includes structures that are directly involved in gas exchange. The respiratory zone begins where the terminal bronchioles join a **respiratory bronchiole**, the smallest type of bronchiole ([link]), which then leads to an alveolar duct, opening into a cluster of alveoli.

Respiratory Zone



Bronchioles lead to alveolar sacs in the respiratory zone, where gas exchange occurs.

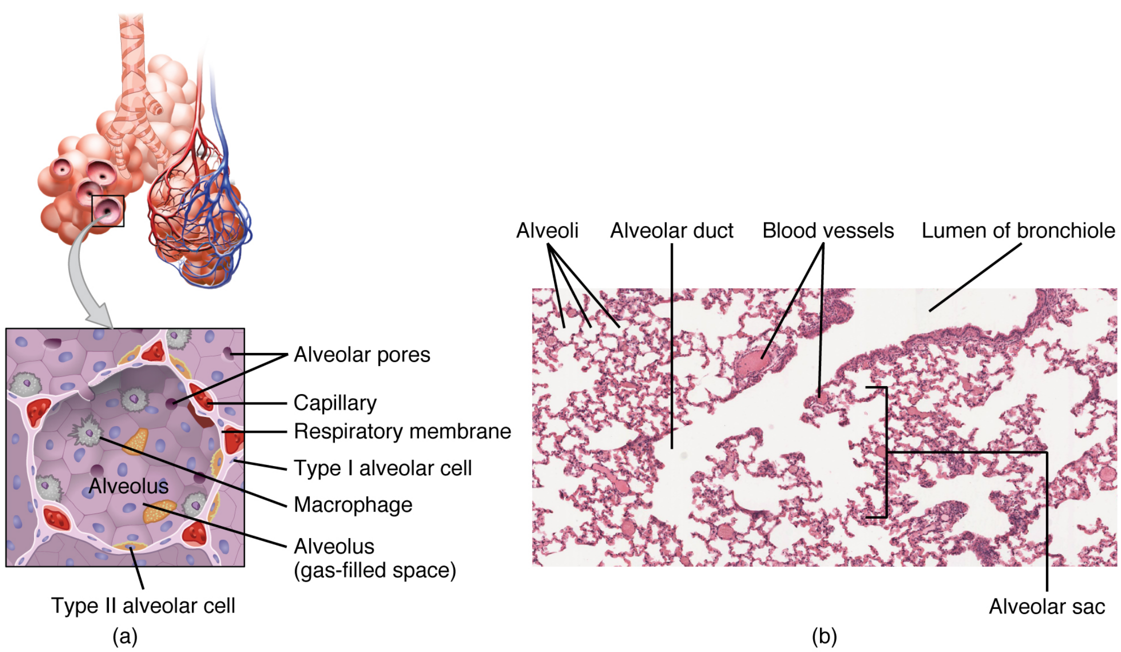
Alveoli

An **alveolar duct** is a tube composed of smooth muscle and connective tissue, which opens into a cluster of alveoli. An **alveolus** is one of the many small, grape-like sacs that are attached to the alveolar ducts.

An **alveolar sac** is a cluster of many individual alveoli that are responsible for gas exchange. An alveolus is approximately 200 μm in diameter with elastic walls that allow the alveolus to stretch during air intake, which greatly increases the surface area available for gas exchange. Alveoli are connected to their neighbors by **alveolar pores**, which help maintain equal air pressure throughout the alveoli and lung ([link]).

Structures of the Respiratory Zone

(a) The alveolus is responsible for gas exchange. (b) A micrograph shows the alveolar structures within lung tissue. LM × 178. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)



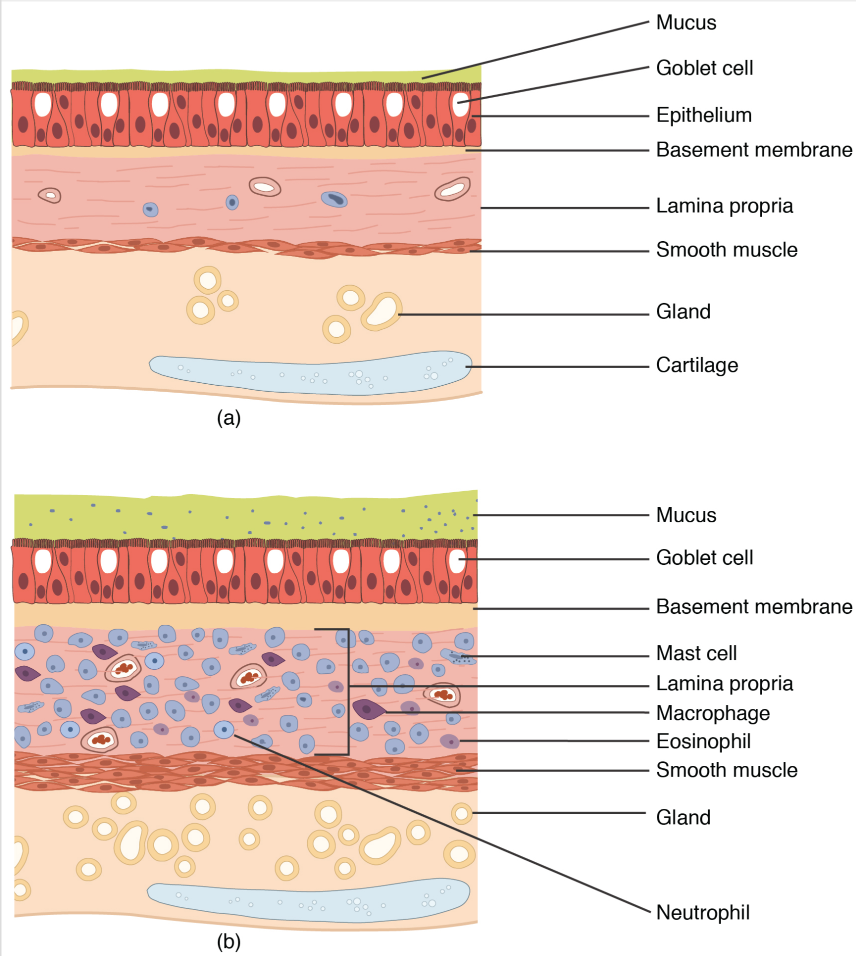
The alveolar wall consists of three major cell types: type I alveolar cells, type II alveolar cells, and alveolar macrophages. A **type I alveolar cell** is a squamous epithelial cell of the alveoli, which constitute up to 97 percent of the alveolar surface area. These cells are about 25 nm thick and are highly permeable to gases. A **type II alveolar cell** is interspersed among the type I cells and secretes **pulmonary surfactant**, a substance composed of phospholipids and proteins that reduces the surface tension of the alveoli. Roaming around the alveolar wall is the **alveolar macrophage**, a phagocytic cell of the immune system that removes debris and pathogens that have reached the alveoli.

The simple squamous epithelium formed by type I alveolar cells is attached to a thin, elastic basement membrane. This epithelium is extremely thin and borders the endothelial membrane of capillaries. Taken together, the alveoli and capillary membranes form a **respiratory membrane** that is approximately 0.5 mm thick. The respiratory membrane allows gases to cross by simple diffusion, allowing oxygen to be picked up by the blood for transport and CO_2 to be released into the air of the alveoli.

Note:
Diseases of the…
Respiratory System: Asthma
Asthma is common condition that affects the lungs in both adults and children. Approximately 8.2 percent of adults (18.7 million) and 9.4 percent of children (7 million) in the United States suffer from asthma. In addition, asthma is the most frequent cause of hospitalization in children.
Asthma is a chronic disease characterized by inflammation and edema of the airway, and bronchospasms (that is, constriction of the bronchioles), which can inhibit air from entering the lungs. In addition, excessive mucus secretion can occur, which further contributes to airway occlusion ([link]). Cells of the immune system, such as eosinophils and mononuclear cells, may also be involved in infiltrating the walls of the bronchi and bronchioles.
Bronchospasms occur periodically and lead to an "asthma attack." An attack may be triggered by environmental factors such as dust, pollen, pet

hair, or dander, changes in the weather, mold, tobacco smoke, and respiratory infections, or by exercise and stress.

Normal and Bronchial Asthma Tissues



(a) Normal lung tissue does not have the characteristics of lung tissue during (b) an asthma attack, which include thickened mucosa, increased mucus-producing goblet cells, and eosinophil infiltrates.

Symptoms of an asthma attack involve coughing, shortness of breath, wheezing, and tightness of the chest. Symptoms of a severe asthma attack that requires immediate medical attention would include difficulty breathing that results in blue (cyanotic) lips or face, confusion, drowsiness, a rapid pulse, sweating, and severe anxiety. The severity of the condition,

frequency of attacks, and identified triggers influence the type of medication that an individual may require. Longer-term treatments are used for those with more severe asthma. Short-term, fast-acting drugs that are used to treat an asthma attack are typically administered via an inhaler. For young children or individuals who have difficulty using an inhaler, asthma medications can be administered via a nebulizer.

In many cases, the underlying cause of the condition is unknown. However, recent research has demonstrated that certain viruses, such as human rhinovirus C (HRVC), and the bacteria *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* that are contracted in infancy or early childhood, may contribute to the development of many cases of asthma.

Note:

Visit this site to learn more about what happens during an asthma attack. What are the three changes that occur inside the airways during an asthma attack?

Chapter Review

The respiratory system is responsible for obtaining oxygen and getting rid of carbon dioxide, and aiding in speech production and in sensing odors. From a functional perspective, the respiratory system can be divided into two major areas: the conducting zone and the respiratory zone. The conducting zone consists of all of the structures that provide passageways for air to travel into and out of the lungs: the nasal cavity, pharynx, trachea, bronchi, and most bronchioles. The nasal passages contain the conchae and

meatuses that expand the surface area of the cavity, which helps to warm and humidify incoming air, while removing debris and pathogens. The pharynx is composed of three major sections: the nasopharynx, which is continuous with the nasal cavity; the oropharynx, which borders the nasopharynx and the oral cavity; and the laryngopharynx, which borders the oropharynx, trachea, and esophagus. The respiratory zone includes the structures of the lung that are directly involved in gas exchange: the terminal bronchioles and alveoli.

The lining of the conducting zone is composed mostly of pseudostratified ciliated columnar epithelium with goblet cells. The mucus traps pathogens and debris, whereas beating cilia move the mucus superiorly toward the throat, where it is swallowed. As the bronchioles become smaller and smaller, and nearer the alveoli, the epithelium thins and is simple squamous epithelium in the alveoli. The endothelium of the surrounding capillaries, together with the alveolar epithelium, forms the respiratory membrane. This is a blood-air barrier through which gas exchange occurs by simple diffusion.

Interactive Link Questions

Exercise:

Problem:

Visit this site to learn more about what happens during an asthma attack. What are the three changes that occur inside the airways during an asthma attack?

Solution:

Inflammation and the production of a thick mucus; constriction of the airway muscles, or bronchospasm; and an increased sensitivity to allergens.

Review Questions

Exercise:

Problem:

Which of the following anatomical structures is *not* part of the conducting zone?

a. pharynx
b. nasal cavity
c. alveoli
d. bronchi

Solution:

C

Exercise:

Problem: What is the function of the conchae in the nasal cavity?

a. increase surface area
b. exchange gases
c. maintain surface tension
d. maintain air pressure

Solution:

A

Exercise:

Problem:

The fauces connects which of the following structures to the oropharynx?

a. nasopharynx
b. laryngopharynx

c. nasal cavity
d. oral cavity

Solution:

D

Exercise:

Problem: Which of the following are structural features of the trachea?

a. C-shaped cartilage
b. smooth muscle fibers
c. cilia
d. all of the above

Solution:

A

Exercise:

Problem:

Which of the following structures is *not* part of the bronchial tree?

a. alveoli
b. bronchi
c. terminal bronchioles
d. respiratory bronchioles

Solution:

C

Exercise:

Problem: What is the role of alveolar macrophages?

a. to secrete pulmonary surfactant
b. to secrete antimicrobial proteins
c. to remove pathogens and debris
d. to facilitate gas exchange

Solution:

C

Critical Thinking Questions

Exercise:

Problem: Describe the three regions of the pharynx and their functions.

Solution:

The pharynx has three major regions. The first region is the nasopharynx, which is connected to the posterior nasal cavity and functions as an airway. The second region is the oropharynx, which is continuous with the nasopharynx and is connected to the oral cavity at the fauces. The laryngopharynx is connected to the oropharynx and the esophagus and trachea. Both the oropharynx and laryngopharynx are passageways for air and food and drink.

Exercise:

Problem:

If a person sustains an injury to the epiglottis, what would be the physiological result?

Solution:

The epiglottis is a region of the larynx that is important during the swallowing of food or drink. As a person swallows, the pharynx moves upward and the epiglottis closes over the trachea, preventing food or drink from entering the trachea. If a person’s epiglottis were injured, this mechanism would be impaired. As a result, the person may have problems with food or drink entering the trachea, and possibly, the lungs. Over time, this may cause infections such as pneumonia to set in.

Exercise:

Problem: Compare and contrast the conducting and respiratory zones.

Solution:

The conducting zone of the respiratory system includes the organs and structures that are not directly involved in gas exchange, but perform other duties such as providing a passageway for air, trapping and removing debris and pathogens, and warming and humidifying incoming air. Such structures include the nasal cavity, pharynx, larynx, trachea, and most of the bronchial tree. The respiratory zone includes all the organs and structures that are directly involved in gas exchange, including the respiratory bronchioles, alveolar ducts, and alveoli.

References

Bizzintino J, Lee WM, Laing IA, Vang F, Pappas T, Zhang G, Martin AC, Khoo SK, Cox DW, Geelhoed GC, et al. Association between human rhinovirus C and severity of acute asthma in children. Eur Respir J [Internet]. 2010 [cited 2013 Mar 22]; 37(5):1037–1042. Available from: http://erj.ersjournals.com/gca?submit=Go&gca=erj%3B37%2F5%2F1037&allch=

Kumar V, Ramzi S, Robbins SL. Robbins Basic Pathology. 7th ed. Philadelphia (PA): Elsevier Ltd; 2005.

Martin RJ, Kraft M, Chu HW, Berns, EA, Cassell GH. A link between chronic asthma and chronic infection. J Allergy Clin Immunol [Internet]. 2001 [cited 2013 Mar 22]; 107(4):595-601. Available from: http://erj.ersjournals.com/gca?submit=Go&gca=erj%3B37%2F5%2F1037&allch=

Glossary

ala
: (plural = alae) small, flaring structure of a nostril that forms the lateral side of the nares

alar cartilage
: cartilage that supports the apex of the nose and helps shape the nares; it is connected to the septal cartilage and connective tissue of the alae

alveolar duct
: small tube that leads from the terminal bronchiole to the respiratory bronchiole and is the point of attachment for alveoli

alveolar macrophage
: immune system cell of the alveolus that removes debris and pathogens

alveolar pore
: opening that allows airflow between neighboring alveoli

alveolar sac
: cluster of alveoli

alveolus
: small, grape-like sac that performs gas exchange in the lungs

apex
: tip of the external nose

bronchial tree
: collective name for the multiple branches of the bronchi and bronchioles of the respiratory system

bridge
: portion of the external nose that lies in the area of the nasal bones

bronchiole
: branch of bronchi that are 1 mm or less in diameter and terminate at alveolar sacs

bronchus
: tube connected to the trachea that branches into many subsidiaries and provides a passageway for air to enter and leave the lungs

conducting zone
: region of the respiratory system that includes the organs and structures that provide passageways for air and are not directly involved in gas exchange

cricoid cartilage
: portion of the larynx composed of a ring of cartilage with a wide posterior region and a thinner anterior region; attached to the esophagus

dorsum nasi
: intermediate portion of the external nose that connects the bridge to the apex and is supported by the nasal bone

epiglottis
: leaf-shaped piece of elastic cartilage that is a portion of the larynx that swings to close the trachea during swallowing

external nose
: region of the nose that is easily visible to others

fauces
: portion of the posterior oral cavity that connects the oral cavity to the oropharynx

fibroelastic membrane

specialized membrane that connects the ends of the C-shape cartilage in the trachea; contains smooth muscle fibers

glottis
: opening between the vocal folds through which air passes when producing speech

laryngeal prominence
: region where the two lamina of the thyroid cartilage join, forming a protrusion known as “Adam’s apple”

laryngopharynx
: portion of the pharynx bordered by the oropharynx superiorly and esophagus and trachea inferiorly; serves as a route for both air and food

larynx
: cartilaginous structure that produces the voice, prevents food and beverages from entering the trachea, and regulates the volume of air that enters and leaves the lungs

lingual tonsil
: lymphoid tissue located at the base of the tongue

meatus
: one of three recesses (superior, middle, and inferior) in the nasal cavity attached to the conchae that increase the surface area of the nasal cavity

naris
: (plural = nares) opening of the nostrils

nasal bone
: bone of the skull that lies under the root and bridge of the nose and is connected to the frontal and maxillary bones

nasal septum

wall composed of bone and cartilage that separates the left and right nasal cavities

nasopharynx
: portion of the pharynx flanked by the conchae and oropharynx that serves as an airway

oropharynx
: portion of the pharynx flanked by the nasopharynx, oral cavity, and laryngopharynx that is a passageway for both air and food

palatine tonsil
: one of the paired structures composed of lymphoid tissue located anterior to the uvula at the roof of isthmus of the fauces

paranasal sinus
: one of the cavities within the skull that is connected to the conchae that serve to warm and humidify incoming air, produce mucus, and lighten the weight of the skull; consists of frontal, maxillary, sphenoidal, and ethmoidal sinuses

pharyngeal tonsil
: structure composed of lymphoid tissue located in the nasopharynx

pharynx
: region of the conducting zone that forms a tube of skeletal muscle lined with respiratory epithelium; located between the nasal conchae and the esophagus and trachea

philtrum
: concave surface of the face that connects the apex of the nose to the top lip

pulmonary surfactant
: substance composed of phospholipids and proteins that reduces the surface tension of the alveoli; made by type II alveolar cells

respiratory bronchiole

specific type of bronchiole that leads to alveolar sacs

respiratory epithelium
: ciliated lining of much of the conducting zone that is specialized to remove debris and pathogens, and produce mucus

respiratory membrane
: alveolar and capillary wall together, which form an air-blood barrier that facilitates the simple diffusion of gases

respiratory zone
: includes structures of the respiratory system that are directly involved in gas exchange

root
: region of the external nose between the eyebrows

thyroid cartilage
: largest piece of cartilage that makes up the larynx and consists of two lamina

trachea
: tube composed of cartilaginous rings and supporting tissue that connects the lung bronchi and the larynx; provides a route for air to enter and exit the lung

trachealis muscle
: smooth muscle located in the fibroelastic membrane of the trachea

true vocal cord
: one of the pair of folded, white membranes that have a free inner edge that oscillates as air passes through to produce sound

type I alveolar cell
: squamous epithelial cells that are the major cell type in the alveolar wall; highly permeable to gases

type II alveolar cell

cuboidal epithelial cells that are the minor cell type in the alveolar wall; secrete pulmonary surfactant

vestibular fold
: part of the folded region of the glottis composed of mucous membrane; supports the epiglottis during swallowing

The Lungs

By the end of this section, you will be able to:

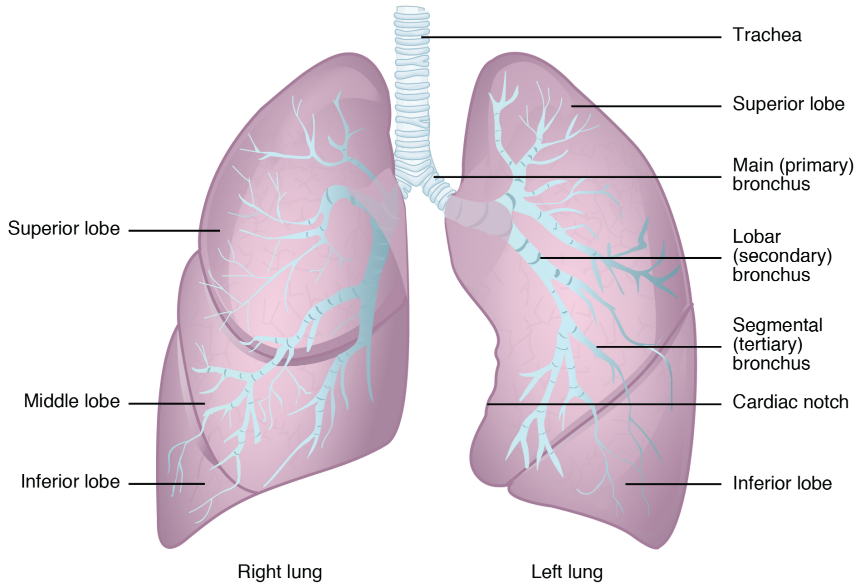
- Describe the overall function of the lung
- Summarize the blood flow pattern associated with the lungs
- Outline the anatomy of the blood supply to the lungs
- Describe the pleura of the lungs and their function

A major organ of the respiratory system, each **lung** houses structures of both the conducting and respiratory zones. The main function of the lungs is to perform the exchange of oxygen and carbon dioxide with air from the atmosphere. To this end, the lungs exchange respiratory gases across a very large epithelial surface area—about 70 square meters—that is highly permeable to gases.

Gross Anatomy of the Lungs

The lungs are pyramid-shaped, paired organs that are connected to the trachea by the right and left bronchi; on the inferior surface, the lungs are bordered by the diaphragm. The diaphragm is the flat, dome-shaped muscle located at the base of the lungs and thoracic cavity. The lungs are enclosed by the pleurae, which are attached to the mediastinum. The right lung is shorter and wider than the left lung, and the left lung occupies a smaller volume than the right. The **cardiac notch** is an indentation on the surface of the left lung, and it allows space for the heart ([link]). The apex of the lung is the superior region, whereas the base is the opposite region near the diaphragm. The costal surface of the lung borders the ribs. The mediastinal surface faces the midline.

Gross Anatomy of the Lungs



Each lung is composed of smaller units called lobes. Fissures separate these lobes from each other. The right lung consists of three lobes: the superior, middle, and inferior lobes. The left lung consists of two lobes: the superior and inferior lobes. A bronchopulmonary segment is a division of a lobe, and each lobe houses multiple bronchopulmonary segments. Each segment receives air from its own tertiary bronchus and is supplied with blood by its own artery. Some diseases of the lungs typically affect one or more bronchopulmonary segments, and in some cases, the diseased segments can be surgically removed with little influence on neighboring segments. A pulmonary lobule is a subdivision formed as the bronchi branch into bronchioles. Each lobule receives its own large bronchiole that has multiple branches. An interlobular septum is a wall, composed of connective tissue, which separates lobules from one another.

Blood Supply and Nervous Innervation of the Lungs

The blood supply of the lungs plays an important role in gas exchange and serves as a transport system for gases throughout the body. In addition, innervation by the both the parasympathetic and sympathetic nervous systems provides an important level of control through dilation and constriction of the airway.

Blood Supply

The major function of the lungs is to perform gas exchange, which requires blood from the pulmonary circulation. This blood supply contains deoxygenated blood and travels to the lungs where erythrocytes, also known as red blood cells, pick up oxygen to be transported to tissues throughout the body. The **pulmonary artery** is an artery that arises from the pulmonary trunk and carries deoxygenated, arterial blood to the alveoli. The pulmonary artery branches multiple times as it follows the bronchi, and each branch becomes progressively smaller in diameter. One arteriole and an accompanying venule supply and drain one pulmonary lobule. As they near the alveoli, the pulmonary arteries become the pulmonary capillary network. The pulmonary capillary network consists of tiny vessels with very thin walls that lack smooth muscle fibers. The capillaries branch and follow the bronchioles and structure of the alveoli. It is at this point that the capillary wall meets the alveolar wall, creating the respiratory membrane. Once the blood is oxygenated, it drains from the alveoli by way of multiple pulmonary veins, which exit the lungs through the **hilum**.

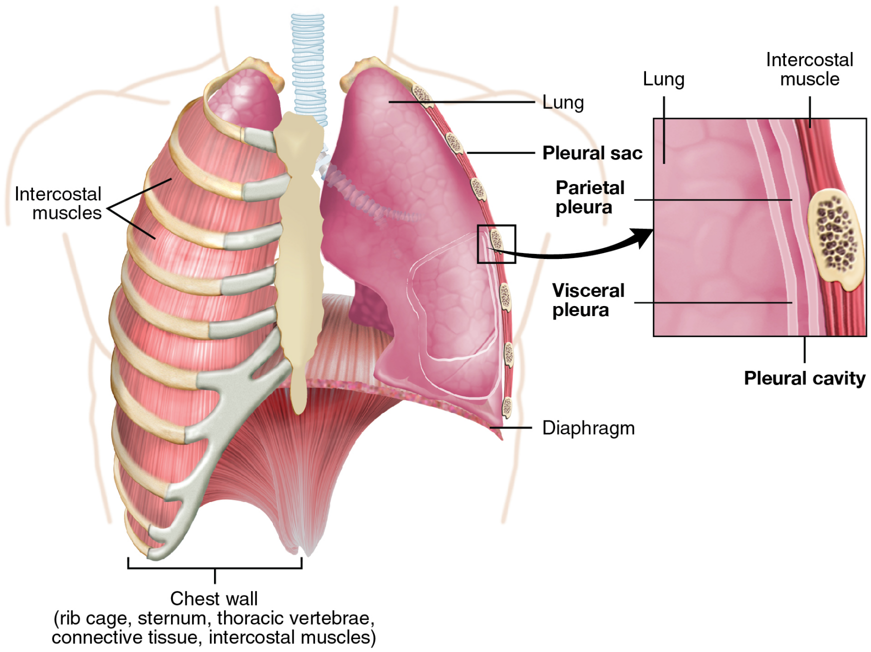
Nervous Innervation

Dilation and constriction of the airway are achieved through nervous control by the parasympathetic and sympathetic nervous systems. The parasympathetic system causes **bronchoconstriction**, whereas the sympathetic nervous system stimulates **bronchodilation**. Reflexes such as coughing, and the ability of the lungs to regulate oxygen and carbon dioxide levels, also result from this autonomic nervous system control. Sensory nerve fibers arise from the vagus nerve, and from the second to fifth thoracic ganglia. The **pulmonary plexus** is a region on the lung root formed by the entrance of the nerves at the hilum. The nerves then follow the bronchi in the lungs and branch to innervate muscle fibers, glands, and blood vessels.

Pleura of the Lungs

Each lung is enclosed within a cavity that is surrounded by the pleura. The pleura (plural = pleurae) is a serous membrane that surrounds the lung. The right and left pleurae, which enclose the right and left lungs, respectively, are separated by the mediastinum. The pleurae consist of two layers. The **visceral pleura** is the layer that is superficial to the lungs, and extends into and lines the lung fissures ([link]). In contrast, the **parietal pleura** is the outer layer that connects to the thoracic wall, the mediastinum, and the diaphragm. The visceral and parietal pleurae connect to each other at the hilum. The **pleural cavity** is the space between the visceral and parietal layers.

Parietal and Visceral Pleurae of the Lungs



The pleurae perform two major functions: They produce pleural fluid and create cavities that separate the major organs. **Pleural fluid** is secreted by mesothelial cells from both pleural layers and acts to lubricate their surfaces. This lubrication reduces friction between the two layers to prevent trauma during breathing, and creates surface tension that helps maintain the position of the lungs against the thoracic wall. This adhesive characteristic of the pleural fluid causes the lungs to enlarge when the thoracic wall expands during ventilation, allowing the lungs to fill with air. The pleurae also create a division between major organs that prevents interference due to the movement of the organs, while preventing the spread of infection.

Note:
Everyday Connection
The Effects of Second-Hand Tobacco Smoke
The burning of a tobacco cigarette creates multiple chemical compounds that are released through mainstream smoke, which is inhaled by the smoker, and through sidestream smoke, which is the smoke that is given off by the burning cigarette. Second-hand smoke, which is a combination of sidestream smoke and the mainstream smoke that is exhaled by the smoker, has been demonstrated by numerous scientific studies to cause disease. At least 40 chemicals in sidestream smoke have been identified that negatively impact human health, leading to the development of cancer or other conditions, such as immune system dysfunction, liver toxicity, cardiac arrhythmias, pulmonary edema, and neurological dysfunction. Furthermore, second-hand smoke has been found to harbor at least 250 compounds that are known to be toxic, carcinogenic, or both. Some major classes of carcinogens in second-hand smoke are polyaromatic hydrocarbons (PAHs), N-nitrosamines, aromatic amines, formaldehyde, and acetaldehyde.
Tobacco and second-hand smoke are considered to be carcinogenic. Exposure to second-hand smoke can cause lung cancer in individuals who are not tobacco users themselves. It is estimated that the risk of developing lung cancer is increased by up to 30 percent in nonsmokers who live with an individual who smokes in the house, as compared to nonsmokers who are not regularly exposed to second-hand smoke. Children are especially affected by second-hand smoke. Children who live with an individual who smokes inside the home have a larger number of lower respiratory infections, which are associated with hospitalizations, and higher risk of sudden infant death syndrome (SIDS). Second-hand smoke in the home has also been linked to a greater number of ear infections in children, as well as worsening symptoms of asthma.

Chapter Review

The lungs are the major organs of the respiratory system and are responsible for performing gas exchange. The lungs are paired and separated into lobes;

The left lung consists of two lobes, whereas the right lung consists of three lobes. Blood circulation is very important, as blood is required to transport oxygen from the lungs to other tissues throughout the body. The function of the pulmonary circulation is to aid in gas exchange. The pulmonary artery provides deoxygenated blood to the capillaries that form respiratory membranes with the alveoli, and the pulmonary veins return newly oxygenated blood to the heart for further transport throughout the body. The lungs are innervated by the parasympathetic and sympathetic nervous systems, which coordinate the bronchodilation and bronchoconstriction of the airways. The lungs are enclosed by the pleura, a membrane that is composed of visceral and parietal pleural layers. The space between these two layers is called the pleural cavity. The mesothelial cells of the pleural membrane create pleural fluid, which serves as both a lubricant (to reduce friction during breathing) and as an adhesive to adhere the lungs to the thoracic wall (to facilitate movement of the lungs during ventilation).

Review Questions

Exercise:

Problem:

Which of the following structures separates the lung into lobes?

a. mediastinum
b. fissure
c. root
d. pleura

Solution:

B

Exercise:

Problem:

A section of the lung that receives its own tertiary bronchus is called the _________.

a. bronchopulmonary segment
b. pulmonary lobule
c. interpulmonary segment
d. respiratory segment

Solution:

A

Exercise:

Problem:

The _________ circulation picks up oxygen for cellular use and drops off carbon dioxide for removal from the body.

a. pulmonary
b. interlobular
c. respiratory
d. bronchial

Solution:

C

Exercise:

Problem:

The pleura that surrounds the lungs consists of two layers, the _________.

a. visceral and parietal pleurae.

b. mediastinum and parietal pleurae.
c. visceral and mediastinum pleurae.
d. none of the above

Solution:

A

Critical Thinking Questions

Exercise:

Problem: Compare and contrast the right and left lungs.

Solution:

The right and left lungs differ in size and shape to accommodate other organs that encroach on the thoracic region. The right lung consists of three lobes and is shorter than the left lung, due to the position of the liver underneath it. The left lung consist of two lobes and is longer and narrower than the right lung. The left lung has a concave region on the mediastinal surface called the cardiac notch that allows space for the heart.

Exercise:

Problem: Why are the pleurae not damaged during normal breathing?

Solution:

There is a cavity, called the pleural cavity, between the parietal and visceral layers of the pleura. Mesothelial cells produce and secrete pleural fluid into the pleural cavity that acts as a lubricant. Therefore, as you breathe, the pleural fluid prevents the two layers of the pleura from rubbing against each other and causing damage due to friction.

Glossary

bronchoconstriction
: decrease in the size of the bronchiole due to contraction of the muscular wall

bronchodilation
: increase in the size of the bronchiole due to contraction of the muscular wall

cardiac notch
: indentation on the surface of the left lung that allows space for the heart

hilum
: concave structure on the mediastinal surface of the lungs where blood vessels, lymphatic vessels, nerves, and a bronchus enter the lung

lung
: organ of the respiratory system that performs gas exchange

parietal pleura
: outermost layer of the pleura that connects to the thoracic wall, mediastinum, and diaphragm

pleural cavity
: space between the visceral and parietal pleurae

pleural fluid
: substance that acts as a lubricant for the visceral and parietal layers of the pleura during the movement of breathing

pulmonary artery
: artery that arises from the pulmonary trunk and carries deoxygenated, arterial blood to the alveoli

pulmonary plexus

network of autonomic nervous system fibers found near the hilum of the lung

visceral pleura
innermost layer of the pleura that is superficial to the lungs and extends into the lung fissures

The Process of Breathing
By the end of this section, you will be able to:

- Describe the mechanisms that drive breathing
- Discuss how pressure, volume, and resistance are related
- List the steps involved in pulmonary ventilation
- Discuss the physical factors related to breathing
- Discuss the meaning of respiratory volume and capacities
- Define respiratory rate
- Outline the mechanisms behind the control of breathing
- Describe the respiratory centers of the medulla oblongata
- Describe the respiratory centers of the pons
- Discuss factors that can influence the respiratory rate

Pulmonary ventilation is the act of breathing, which can be described as the movement of air into and out of the lungs. The major mechanisms that drive pulmonary ventilation are atmospheric pressure (P_{atm}); the air pressure within the alveoli, called intra-alveolar pressure (P_{alv}); and the pressure within the pleural cavity, called intrapleural pressure (P_{ip}).

Mechanisms of Breathing

The intra-alveolar and intrapleural pressures are dependent on certain physical features of the lung. However, the ability to breathe—to have air enter the lungs during inspiration and air leave the lungs during expiration—is dependent on the air pressure of the atmosphere and the air pressure within the lungs.

Pressure Relationships

Inspiration (or inhalation) and expiration (or exhalation) are dependent on the differences in pressure between the atmosphere and the lungs. In a gas, pressure is a force created by the movement of gas molecules that are confined. For example, a certain number of gas molecules in a two-liter container has more room than the same number of gas molecules in a one-liter container ([link]). In this case, the force exerted by the movement of

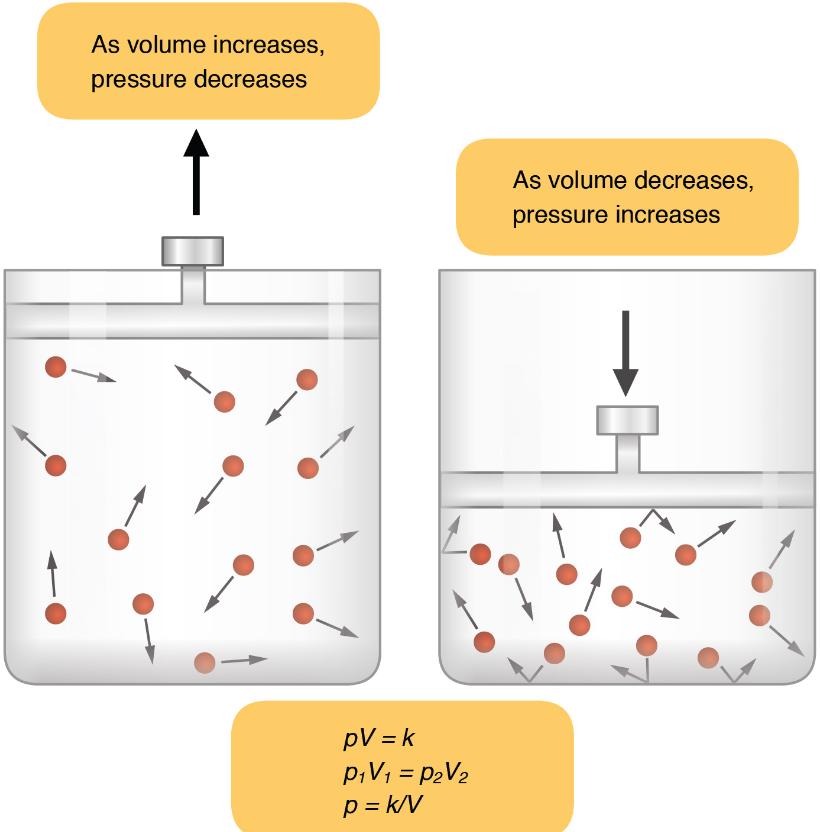
the gas molecules against the walls of the two-liter container is lower than the force exerted by the gas molecules in the one-liter container. Therefore, the pressure is lower in the two-liter container and higher in the one-liter container. At a constant temperature, changing the volume occupied by the gas changes the pressure, as does changing the number of gas molecules. **Boyle's law** describes the relationship between volume and pressure in a gas at a constant temperature. Boyle discovered that the pressure of a gas is inversely proportional to its volume: If volume increases, pressure decreases. Likewise, if volume decreases, pressure increases. Pressure and volume are inversely related (P = k/V). Therefore, the pressure in the one-liter container (one-half the volume of the two-liter container) would be twice the pressure in the two-liter container. Boyle's law is expressed by the following formula:

Equation:

$$P_1V_1 = P_2V_2$$

In this formula, P_1 represents the initial pressure and V_1 represents the initial volume, whereas the final pressure and volume are represented by P_2 and V_2, respectively. If the two- and one-liter containers were connected by a tube and the volume of one of the containers were changed, then the gases would move from higher pressure (lower volume) to lower pressure (higher volume).

Boyle's Law

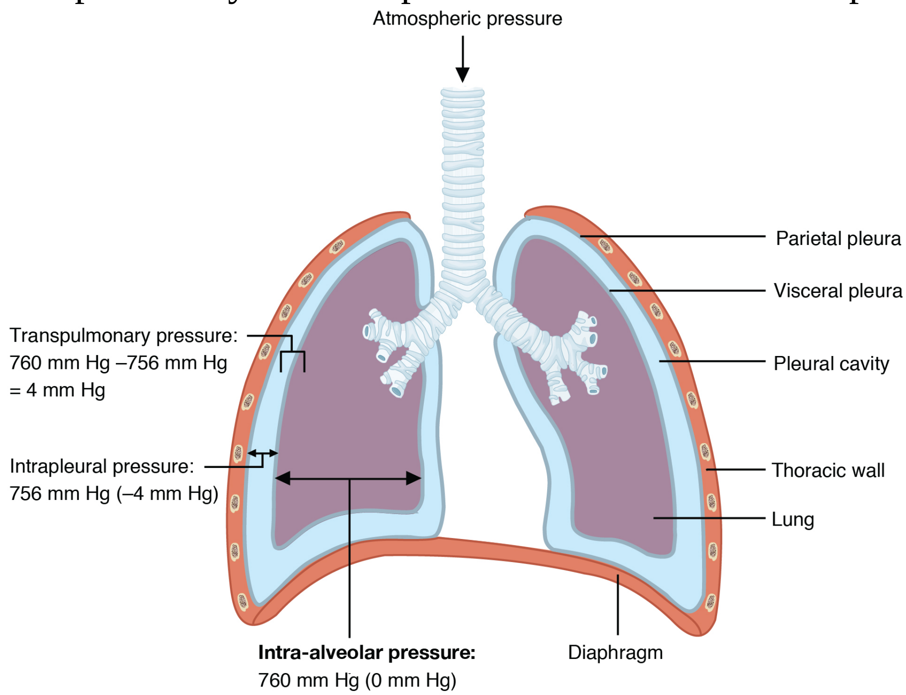


In a gas, pressure increases as volume decreases.

Pulmonary ventilation is dependent on three types of pressure: atmospheric, intra-alveolar, and intrapleural. **Atmospheric pressure** is the amount of force that is exerted by gases in the air surrounding any given surface, such as the body. Atmospheric pressure can be expressed in terms of the unit atmosphere, abbreviated atm, or in millimeters of mercury (mm Hg). One atm is equal to 760 mm Hg, which is the atmospheric pressure at sea level. Typically, for respiration, other pressure values are discussed in relation to atmospheric pressure. Therefore, negative pressure is pressure lower than the atmospheric pressure, whereas positive pressure is pressure that it is greater than the atmospheric pressure. A pressure that is equal to the atmospheric pressure is expressed as zero.

Intra-alveolar pressure (intrapulmonary pressure) is the pressure of the air within the alveoli, which changes during the different phases of breathing ([link]). Because the alveoli are connected to the atmosphere via the tubing of the airways (similar to the two- and one-liter containers in the example above), the intrapulmonary pressure of the alveoli always equalizes with the atmospheric pressure.

Intrapulmonary and Intrapleural Pressure Relationships



Intra-alveolar pressure changes during the different phases of the cycle. It equalizes at 760 mm Hg but does not remain at 760 mm Hg.

Intrapleural pressure is the pressure of the air within the pleural cavity, between the visceral and parietal pleurae. Similar to intra-alveolar pressure, intrapleural pressure also changes during the different phases of breathing. However, due to certain characteristics of the lungs, the intrapleural pressure is always lower than, or negative to, the intra-alveolar pressure (and therefore also to atmospheric pressure). Although it fluctuates during inspiration and expiration, intrapleural pressure remains approximately –4 mm Hg throughout the breathing cycle.

Competing forces within the thorax cause the formation of the negative intrapleural pressure. One of these forces relates to the elasticity of the lungs themselves—elastic tissue pulls the lungs inward, away from the thoracic wall. Surface tension of alveolar fluid, which is mostly water, also creates an inward pull of the lung tissue. This inward tension from the lungs is countered by opposing forces from the pleural fluid and thoracic wall. Surface tension within the pleural cavity pulls the lungs outward. Too much or too little pleural fluid would hinder the creation of the negative intrapleural pressure; therefore, the level must be closely monitored by the mesothelial cells and drained by the lymphatic system. Since the parietal pleura is attached to the thoracic wall, the natural elasticity of the chest wall opposes the inward pull of the lungs. Ultimately, the outward pull is slightly greater than the inward pull, creating the –4 mm Hg intrapleural pressure relative to the intra-alveolar pressure. **Transpulmonary pressure** is the difference between the intrapleural and intra-alveolar pressures, and it determines the size of the lungs. A higher transpulmonary pressure corresponds to a larger lung.

Physical Factors Affecting Ventilation

In addition to the differences in pressures, breathing is also dependent upon the contraction and relaxation of muscle fibers of both the diaphragm and thorax. The lungs themselves are passive during breathing, meaning they are not involved in creating the movement that helps inspiration and expiration. This is because of the adhesive nature of the pleural fluid, which allows the lungs to be pulled outward when the thoracic wall moves during inspiration. The recoil of the thoracic wall during expiration causes compression of the lungs. Contraction and relaxation of the diaphragm and intercostals muscles (found between the ribs) cause most of the pressure changes that result in inspiration and expiration. These muscle movements and subsequent pressure changes cause air to either rush in or be forced out of the lungs.

Other characteristics of the lungs influence the effort that must be expended to ventilate. Resistance is a force that slows motion, in this case, the flow of gases. The size of the airway is the primary factor affecting resistance. A

small tubular diameter forces air through a smaller space, causing more collisions of air molecules with the walls of the airways. The following formula helps to describe the relationship between airway resistance and pressure changes:

Equation:

$$F = \Delta P / R$$

As noted earlier, there is surface tension within the alveoli caused by water present in the lining of the alveoli. This surface tension tends to inhibit expansion of the alveoli. However, pulmonary surfactant secreted by type II alveolar cells mixes with that water and helps reduce this surface tension. Without pulmonary surfactant, the alveoli would collapse during expiration.

Thoracic wall compliance is the ability of the thoracic wall to stretch while under pressure. This can also affect the effort expended in the process of breathing. In order for inspiration to occur, the thoracic cavity must expand. The expansion of the thoracic cavity directly influences the capacity of the lungs to expand. If the tissues of the thoracic wall are not very compliant, it will be difficult to expand the thorax to increase the size of the lungs.

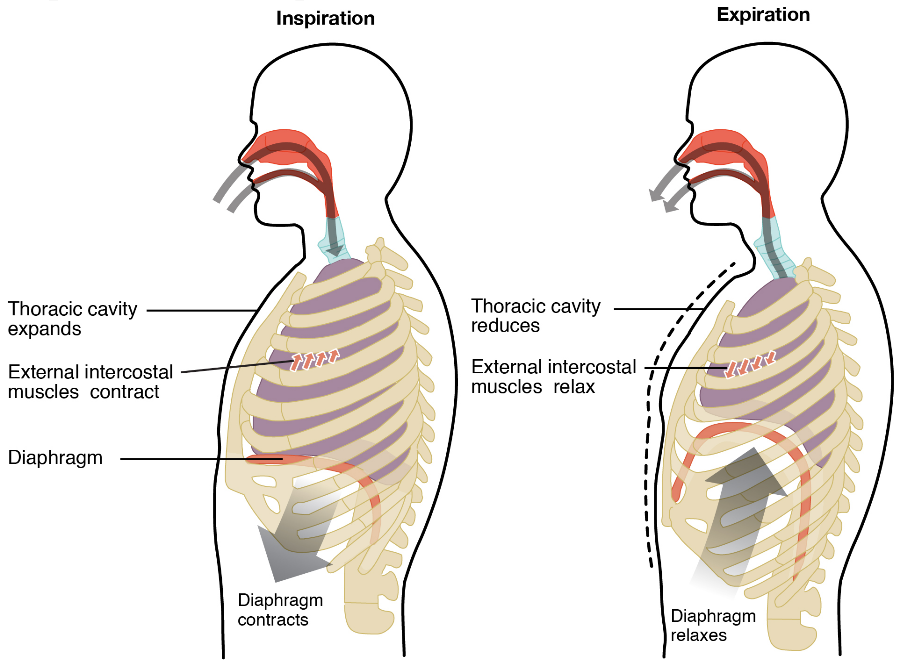
Pulmonary Ventilation

The difference in pressures drives pulmonary ventilation because air flows down a pressure gradient, that is, air flows from an area of higher pressure to an area of lower pressure. Air flows into the lungs largely due to a difference in pressure; atmospheric pressure is greater than intra-alveolar pressure, and intra-alveolar pressure is greater than intrapleural pressure. Air flows out of the lungs during expiration based on the same principle; pressure within the lungs becomes greater than the atmospheric pressure.

Pulmonary ventilation comprises two major steps: inspiration and expiration. **Inspiration** is the process that causes air to enter the lungs, and **expiration** is the process that causes air to leave the lungs ([link]). A **respiratory cycle** is one sequence of inspiration and expiration. In general,

two muscle groups are used during normal inspiration: the diaphragm and the external intercostal muscles. Additional muscles can be used if a bigger breath is required. When the diaphragm contracts, it moves inferiorly toward the abdominal cavity, creating a larger thoracic cavity and more space for the lungs. Contraction of the external intercostal muscles moves the ribs upward and outward, causing the rib cage to expand, which increases the volume of the thoracic cavity. Due to the adhesive force of the pleural fluid, the expansion of the thoracic cavity forces the lungs to stretch and expand as well. This increase in volume leads to a decrease in intra-alveolar pressure, creating a pressure lower than atmospheric pressure. As a result, a pressure gradient is created that drives air into the lungs.

Inspiration and Expiration



Inspiration and expiration occur due to the expansion and contraction of the thoracic cavity, respectively.

The process of normal expiration is passive, meaning that energy is not required to push air out of the lungs. Instead, the elasticity of the lung tissue causes the lung to recoil, as the diaphragm and intercostal muscles relax following inspiration. In turn, the thoracic cavity and lungs decrease in

volume, causing an increase in intrapulmonary pressure. The intrapulmonary pressure rises above atmospheric pressure, creating a pressure gradient that causes air to leave the lungs.

There are different types, or modes, of breathing that require a slightly different process to allow inspiration and expiration. **Quiet breathing**, also known as eupnea, is a mode of breathing that occurs at rest and does not require the cognitive thought of the individual. During quiet breathing, the diaphragm and external intercostals must contract.

A deep breath, called diaphragmatic breathing, requires the diaphragm to contract. As the diaphragm relaxes, air passively leaves the lungs. A shallow breath, called costal breathing, requires contraction of the intercostal muscles. As the intercostal muscles relax, air passively leaves the lungs.

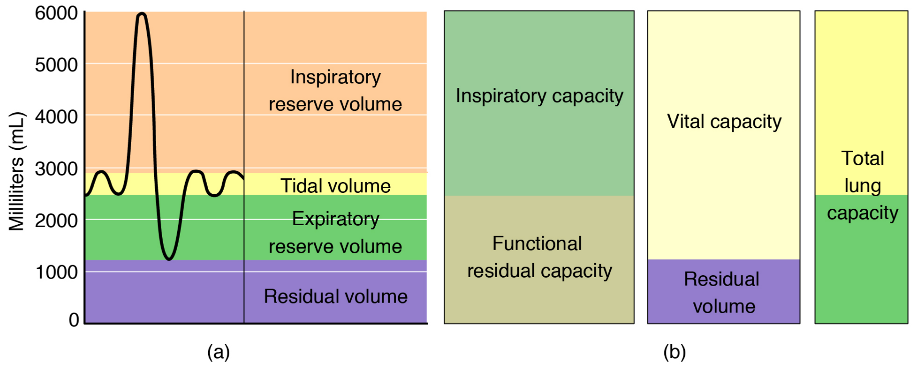
In contrast, **forced breathing**, also known as hyperpnea, is a mode of breathing that can occur during exercise or actions that require the active manipulation of breathing, such as singing. During forced breathing, inspiration and expiration both occur due to muscle contractions. In addition to the contraction of the diaphragm and intercostal muscles, other accessory muscles must also contract. During forced inspiration, muscles of the neck, including the scalenes, contract and lift the thoracic wall, increasing lung volume. During forced expiration, accessory muscles of the abdomen, including the obliques, contract, forcing abdominal organs upward against the diaphragm. This helps to push the diaphragm further into the thorax, pushing more air out. In addition, accessory muscles (primarily the internal intercostals) help to compress the rib cage, which also reduces the volume of the thoracic cavity.

Respiratory Volumes and Capacities

Respiratory volume is the term used for various volumes of air moved by or associated with the lungs at a given point in the respiratory cycle. There are four major types of respiratory volumes: tidal, residual, inspiratory reserve, and expiratory reserve ([link]). **Tidal volume (TV)** is the amount of air that normally enters the lungs during quiet breathing, which is about

500 milliliters. **Expiratory reserve volume (ERV)** is the amount of air you can forcefully exhale past a normal tidal expiration, up to 1200 milliliters for men. **Inspiratory reserve volume (IRV)** is produced by a deep inhalation, past a tidal inspiration. This is the extra volume that can be brought into the lungs during a forced inspiration. **Residual volume (RV)** is the air left in the lungs if you exhale as much air as possible. The residual volume makes breathing easier by preventing the alveoli from collapsing. Respiratory volume is dependent on a variety of factors, and measuring the different types of respiratory volumes can provide important clues about a person's respiratory health ([link]).

Respiratory Volumes and Capacities



These two graphs show (a) respiratory volumes and (b) the combination of volumes that results in respiratory capacity.

Pulmonary Function Testing

Pulmonary function test	Instrument	Measures	Function
Spirometry	Spirometer	Forced vital capacity (FVC)	Volume of air that is exhaled after maximum inhalation
		Forced expiratory volume (FEV)	Volume of air exhaled during one forced breath
		Forced expiratory flow, 25–75 percent	Air flow in the middle of exhalation
		Peak expiratory flow (PEF)	Rate of exhalation
		Maximum voluntary ventilation (MVV)	Volume of air that can be inspired and expired in 1 minute
		Slow vital capacity (SVC)	Volume of air that can be slowly exhaled after inhaling past the tidal volume
		Total lung capacity (TLC)	Volume of air in the lungs after maximum inhalation
		Functional residual capacity (FRC)	Volume of air left in the lungs after normal expiration
		Residual volume (RV)	Volume of air in the lungs after maximum exhalation
		Total lung capacity (TLC)	Maximum volume of air that the lungs can hold
		Expiratory reserve volume (ERV)	The volume of air that can be exhaled beyond normal exhalation
Gas diffusion	Blood gas analyzer	Arterial blood gases	Concentration of oxygen and carbon dioxide in the blood

Respiratory capacity is the combination of two or more selected volumes, which further describes the amount of air in the lungs during a given time. For example, **total lung capacity (TLC)** is the sum of all of the lung volumes (TV, ERV, IRV, and RV), which represents the total amount of air a person can hold in the lungs after a forceful inhalation. TLC is about 6000 mL air for men, and about 4200 mL for women. **Vital capacity (VC)** is the amount of air a person can move into or out of his or her lungs, and is the sum of all of the volumes except residual volume (TV, ERV, and IRV), which is between 4000 and 5000 milliliters. **Inspiratory capacity (IC)** is the maximum amount of air that can be inhaled past a normal tidal expiration, is the sum of the tidal volume and inspiratory reserve volume. On the other hand, the **functional residual capacity (FRC)** is the amount of air that remains in the lung after a normal tidal expiration; it is the sum of expiratory reserve volume and residual volume (see [link]).

Note:

Watch this video to learn more about lung volumes and spirometers. Explain how spirometry test results can be used to diagnose respiratory diseases or determine the effectiveness of disease treatment.

In addition to the air that creates respiratory volumes, the respiratory system also contains **anatomical dead space**, which is air that is present in the airway that never reaches the alveoli and therefore never participates in gas exchange. **Alveolar dead space** involves air found within alveoli that are unable to function, such as those affected by disease or abnormal blood flow. **Total dead space** is the anatomical dead space and alveolar dead space together, and represents all of the air in the respiratory system that is not being used in the gas exchange process.

Respiratory Rate and Control of Ventilation

Breathing usually occurs without thought, although at times you can consciously control it, such as when you swim under water, sing a song, or blow bubbles. The **respiratory rate** is the total number of breaths, or respiratory cycles, that occur each minute. Respiratory rate can be an important indicator of disease, as the rate may increase or decrease during an illness or in a disease condition. The respiratory rate is controlled by the respiratory center located within the medulla oblongata in the brain, which responds primarily to changes in carbon dioxide, oxygen, and pH levels in the blood.

The normal respiratory rate of a child decreases from birth to adolescence. A child under 1 year of age has a normal respiratory rate between 30 and 60 breaths per minute, but by the time a child is about 10 years old, the normal

rate is closer to 18 to 30. By adolescence, the normal respiratory rate is similar to that of adults, 12 to 18 breaths per minute.

Ventilation Control Centers

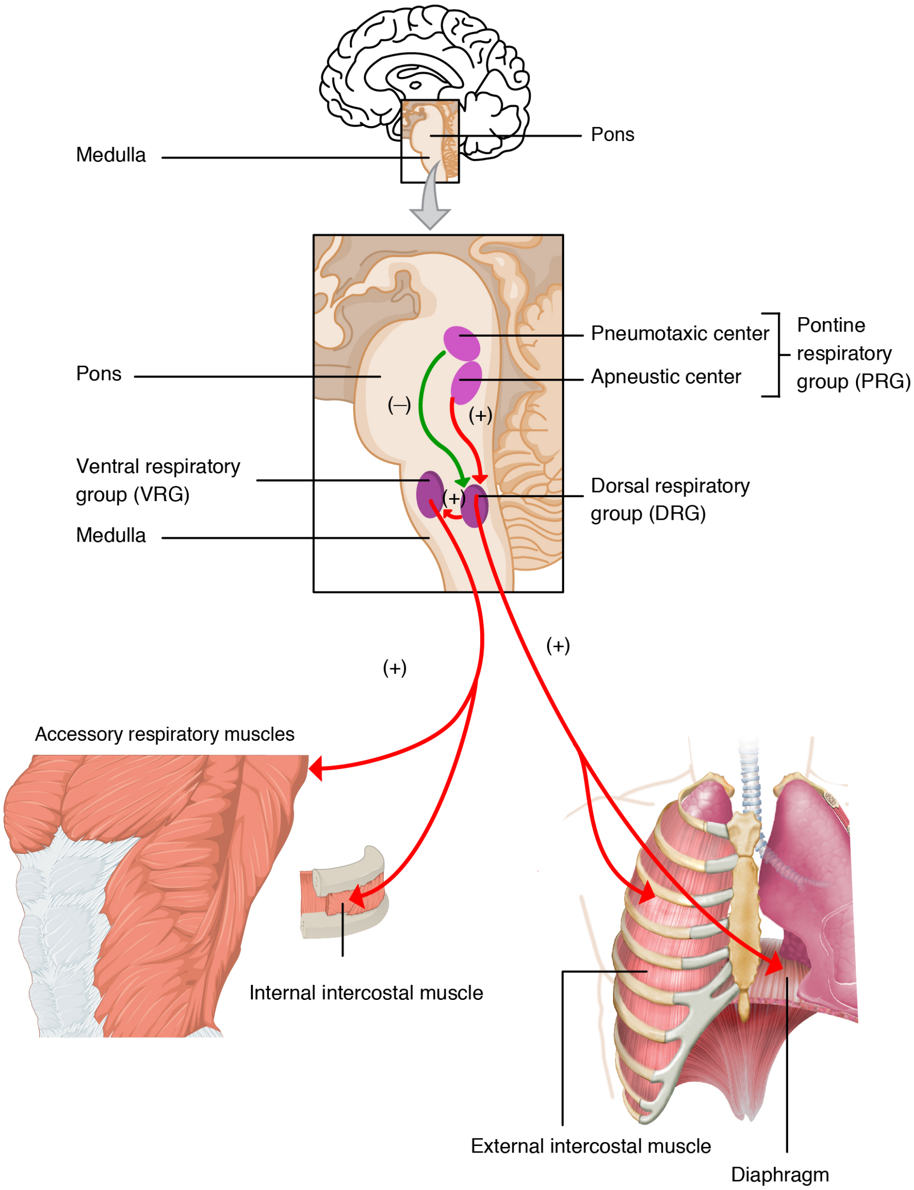
The control of ventilation is a complex interplay of multiple regions in the brain that signal the muscles used in pulmonary ventilation to contract ([link]). The result is typically a rhythmic, consistent ventilation rate that provides the body with sufficient amounts of oxygen, while adequately removing carbon dioxide.

Summary of Ventilation Regulation	
System component	**Function**
Medullary respiratory renter	Sets the basic rhythm of breathing
Ventral respiratory group (VRG)	Generates the breathing rhythm and integrates data coming into the medulla
Dorsal respiratory group (DRG)	Integrates input from the stretch receptors and the chemoreceptors in the periphery
Pontine respiratory group (PRG)	Influences and modifies the medulla oblongata’s functions

Summary of Ventilation Regulation	
System component	**Function**
Aortic body	Monitors blood PCO_2, PO_2, and pH
Carotid body	Monitors blood PCO_2, PO_2, and pH
Hypothalamus	Monitors emotional state and body temperature
Cortical areas of the brain	Control voluntary breathing
Proprioceptors	Send impulses regarding joint and muscle movements
Pulmonary irritant reflexes	Protect the respiratory zones of the system from foreign material
Inflation reflex	Protects the lungs from over-inflating

Neurons that innervate the muscles of the respiratory system are responsible for controlling and regulating pulmonary ventilation. The major brain centers involved in pulmonary ventilation are the medulla oblongata and the pontine respiratory group ([link]).

Respiratory Centers of the Brain



The medulla oblongata contains the **dorsal respiratory group (DRG)** and the **ventral respiratory group (VRG)**. The DRG is involved in maintaining a constant breathing rhythm by stimulating the diaphragm and intercostal muscles to contract, resulting in inspiration. When activity in the DRG ceases, it no longer stimulates the diaphragm and intercostals to contract, allowing them to relax, resulting in expiration. The VRG is involved in forced breathing, as the neurons in the VRG stimulate the accessory muscles involved in forced breathing to contract, resulting in forced inspiration. The VRG also stimulates the accessory muscles involved in forced expiration to contract.

The second respiratory center of the brain is located within the pons, called the pontine respiratory group, and consists of the apneustic and pneumotaxic centers. The **apneustic center** is a double cluster of neuronal cell bodies that stimulate neurons in the DRG, controlling the depth of inspiration, particularly for deep breathing. The **pneumotaxic center** is a network of neurons that inhibits the activity of neurons in the DRG, allowing relaxation after inspiration, and thus controlling the overall rate.

Factors That Affect the Rate and Depth of Respiration

The respiratory rate and the depth of inspiration are regulated by the medulla oblongata and pons; however, these regions of the brain do so in response to systemic stimuli. It is a dose-response, negative-feedback relationship in which the greater the stimulus, the greater the response. Thus, increasing stimuli results in forced breathing. Multiple systemic factors are involved in stimulating the brain to produce pulmonary ventilation.

The major factor that stimulates the medulla oblongata and pons to produce respiration is surprisingly not oxygen concentration, but rather the concentration of carbon dioxide in the blood. As you recall, carbon dioxide is a waste product of cellular respiration and can be toxic. Concentrations of chemicals are sensed by chemoreceptors. A **central chemoreceptor** is one of the specialized receptors that are located in the brain and brainstem, whereas a **peripheral chemoreceptor** is one of the specialized receptors located in the carotid arteries and aortic arch. Concentration changes in certain substances, such as carbon dioxide or hydrogen ions, stimulate these receptors, which in turn signal the respiration centers of the brain. In the case of carbon dioxide, as the concentration of CO_2 in the blood increases, it readily diffuses across the blood-brain barrier, where it collects in the extracellular fluid. As will be explained in more detail later, increased carbon dioxide levels lead to increased levels of hydrogen ions, decreasing pH. The increase in hydrogen ions in the brain triggers the central chemoreceptors to stimulate the respiratory centers to initiate contraction of the diaphragm and intercostal muscles. As a result, the rate and depth of respiration increase, allowing more carbon dioxide to be expelled, which

brings more air into and out of the lungs promoting a reduction in the blood levels of carbon dioxide, and therefore hydrogen ions, in the blood. In contrast, low levels of carbon dioxide in the blood cause low levels of hydrogen ions in the brain, leading to a decrease in the rate and depth of pulmonary ventilation, producing shallow, slow breathing.

Another factor involved in influencing the respiratory activity of the brain is systemic arterial concentrations of hydrogen ions. Increasing carbon dioxide levels can lead to increased H^+ levels, as mentioned above, as well as other metabolic activities, such as lactic acid accumulation after strenuous exercise. Peripheral chemoreceptors of the aortic arch and carotid arteries sense arterial levels of hydrogen ions. When peripheral chemoreceptors sense decreasing, or more acidic, pH levels, they stimulate an increase in ventilation to remove carbon dioxide from the blood at a quicker rate. Removal of carbon dioxide from the blood helps to reduce hydrogen ions, thus increasing systemic pH.

Blood levels of oxygen are also important in influencing respiratory rate. The peripheral chemoreceptors are responsible for sensing large changes in blood oxygen levels. If blood oxygen levels become quite low—about 60 mm Hg or less—then peripheral chemoreceptors stimulate an increase in respiratory activity. The chemoreceptors are only able to sense dissolved oxygen molecules, not the oxygen that is bound to hemoglobin. As you recall, the majority of oxygen is bound by hemoglobin; when dissolved levels of oxygen drop, hemoglobin releases oxygen. Therefore, a large drop in oxygen levels is required to stimulate the chemoreceptors of the aortic arch and carotid arteries.

The hypothalamus and other brain regions associated with the limbic system also play roles in influencing the regulation of breathing by interacting with the respiratory centers. The hypothalamus and other regions associated with the limbic system are involved in regulating respiration in response to emotions, pain, and temperature. For example, an increase in body temperature causes an increase in respiratory rate. Feeling excited or the fight-or-flight response will also result in an increase in respiratory rate.

Note:

Disorders of the…

Respiratory System: Sleep Apnea

Sleep apnea is a chronic disorder that can occur in children or adults, and is characterized by the cessation of breathing during sleep. These episodes may last for several seconds or several minutes, and may differ in the frequency with which they are experienced. Sleep apnea leads to poor sleep, which is reflected in the symptoms of fatigue, evening napping, irritability, memory problems, and morning headaches. In addition, many individuals with sleep apnea experience a dry throat in the morning after waking from sleep, which may be due to excessive snoring.

There are two types of sleep apnea: obstructive sleep apnea and central sleep apnea. Obstructive sleep apnea is caused by an obstruction of the airway during sleep, which can occur at different points in the airway, depending on the underlying cause of the obstruction. For example, the tongue and throat muscles of some individuals with obstructive sleep apnea may relax excessively, causing the muscles to push into the airway. Another example is obesity, which is a known risk factor for sleep apnea, as excess adipose tissue in the neck region can push the soft tissues towards the lumen of the airway, causing the trachea to narrow.

In central sleep apnea, the respiratory centers of the brain do not respond properly to rising carbon dioxide levels and therefore do not stimulate the contraction of the diaphragm and intercostal muscles regularly. As a result, inspiration does not occur and breathing stops for a short period. In some cases, the cause of central sleep apnea is unknown. However, some medical conditions, such as stroke and congestive heart failure, may cause damage to the pons or medulla oblongata. In addition, some pharmacologic agents, such as morphine, can affect the respiratory centers, causing a decrease in the respiratory rate. The symptoms of central sleep apnea are similar to those of obstructive sleep apnea.

A diagnosis of sleep apnea is usually done during a sleep study, where the patient is monitored in a sleep laboratory for several nights. The patient's blood oxygen levels, heart rate, respiratory rate, and blood pressure are monitored, as are brain activity and the volume of air that is inhaled and exhaled. Treatment of sleep apnea commonly includes the use of a device called a continuous positive airway pressure (CPAP) machine during sleep. The CPAP machine has a mask that covers the nose, or the nose and

mouth, and forces air into the airway at regular intervals. This pressurized air can help to gently force the airway to remain open, allowing more normal ventilation to occur. Other treatments include lifestyle changes to decrease weight, eliminate alcohol and other sleep apnea–promoting drugs, and changes in sleep position. In addition to these treatments, patients with central sleep apnea may need supplemental oxygen during sleep.

Chapter Review

Pulmonary ventilation is the process of breathing, which is driven by pressure differences between the lungs and the atmosphere. Atmospheric pressure is the force exerted by gases present in the atmosphere. The force exerted by gases within the alveoli is called intra-alveolar (intrapulmonary) pressure, whereas the force exerted by gases in the pleural cavity is called intrapleural pressure. Typically, intrapleural pressure is lower, or negative to, intra-alveolar pressure. The difference in pressure between intrapleural and intra-alveolar pressures is called transpulmonary pressure. In addition, intra-alveolar pressure will equalize with the atmospheric pressure. Pressure is determined by the volume of the space occupied by a gas and is influenced by resistance. Air flows when a pressure gradient is created, from a space of higher pressure to a space of lower pressure. Boyle’s law describes the relationship between volume and pressure. A gas is at lower pressure in a larger volume because the gas molecules have more space to in which to move. The same quantity of gas in a smaller volume results in gas molecules crowding together, producing increased pressure.

Resistance is created by inelastic surfaces, as well as the diameter of the airways. Resistance reduces the flow of gases. The surface tension of the alveoli also influences pressure, as it opposes the expansion of the alveoli. However, pulmonary surfactant helps to reduce the surface tension so that the alveoli do not collapse during expiration. The ability of the lungs to stretch, called lung compliance, also plays a role in gas flow. The more the lungs can stretch, the greater the potential volume of the lungs. The greater the volume of the lungs, the lower the air pressure within the lungs.

Pulmonary ventilation consists of the process of inspiration (or inhalation), where air enters the lungs, and expiration (or exhalation), where air leaves the lungs. During inspiration, the diaphragm and external intercostal muscles contract, causing the rib cage to expand and move outward, and expanding the thoracic cavity and lung volume. This creates a lower pressure within the lung than that of the atmosphere, causing air to be drawn into the lungs. During expiration, the diaphragm and intercostals relax, causing the thorax and lungs to recoil. The air pressure within the lungs increases to above the pressure of the atmosphere, causing air to be forced out of the lungs. However, during forced exhalation, the internal intercostals and abdominal muscles may be involved in forcing air out of the lungs.

Respiratory volume describes the amount of air in a given space within the lungs, or which can be moved by the lung, and is dependent on a variety of factors. Tidal volume refers to the amount of air that enters the lungs during quiet breathing, whereas inspiratory reserve volume is the amount of air that enters the lungs when a person inhales past the tidal volume. Expiratory reserve volume is the extra amount of air that can leave with forceful expiration, following tidal expiration. Residual volume is the amount of air that is left in the lungs after expelling the expiratory reserve volume. Respiratory capacity is the combination of two or more volumes. Anatomical dead space refers to the air within the respiratory structures that never participates in gas exchange, because it does not reach functional alveoli. Respiratory rate is the number of breaths taken per minute, which may change during certain diseases or conditions.

Both respiratory rate and depth are controlled by the respiratory centers of the brain, which are stimulated by factors such as chemical and pH changes in the blood. These changes are sensed by central chemoreceptors, which are located in the brain, and peripheral chemoreceptors, which are located in the aortic arch and carotid arteries. A rise in carbon dioxide or a decline in oxygen levels in the blood stimulates an increase in respiratory rate and depth.

Interactive Link Questions

Exercise:

Problem:

Watch this video to learn more about lung volumes and spirometers. Explain how spirometry test results can be used to diagnose respiratory diseases or determine the effectiveness of disease treatment.

Solution:

Patients with respiratory ailments (such as asthma, emphysema, COPD, etc.) have issues with airway resistance and/or lung compliance. Both of these factors can interfere with the patient's ability to move air effectively. A spirometry test can determine how much air the patient can move into and out of the lungs. If the air volumes are low, this can indicate that the patient has a respiratory disease or that the treatment regimen may need to be adjusted. If the numbers are normal, the patient does not have a significant respiratory disease or the treatment regimen is working as expected.

Review Questions

Exercise:

Problem:

Which of the following processes does atmospheric pressure play a role in?

a. pulmonary ventilation
b. production of pulmonary surfactant
c. resistance
d. surface tension

Solution:

A

Exercise:

Problem:A decrease in volume leads to a(n) _________ pressure.

a. decrease in
b. equalization of
c. increase in
d. zero

Solution:

C

Exercise:

Problem:

The pressure difference between the intra-alveolar and intrapleural pressures is called _________.

a. atmospheric pressure
b. pulmonary pressure
c. negative pressure
d. transpulmonary pressure

Solution:

D

Exercise:

Problem: Gas flow decreases as _________ increases.

a. resistance
b. pressure
c. airway diameter
d. friction

Solution:

A

Exercise:

Problem:

Contraction of the external intercostal muscles causes which of the following to occur?

a. The diaphragm moves downward.
b. The rib cage is compressed.
c. The thoracic cavity volume decreases.
d. The ribs and sternum move upward.

Solution:

D

Exercise:

Problem: Which of the following prevents the alveoli from collapsing?

a. residual volume
b. tidal volume
c. expiratory reserve volume
d. inspiratory reserve volume

Solution:

A

Critical Thinking Questions

Exercise:

Problem: Describe what is meant by the term “lung compliance.”

Solution:

Lung compliance refers to the ability of lung tissue to stretch under pressure, which is determined in part by the surface tension of the alveoli and the ability of the connective tissue to stretch. Lung compliance plays a role in determining how much the lungs can change in volume, which in turn helps to determine pressure and air movement.

Exercise:

Problem: Outline the steps involved in quiet breathing.

Solution:

Quiet breathing occurs at rest and without active thought. During quiet breathing, the diaphragm and external intercostal muscles work at different extents, depending on the situation. For inspiration, the diaphragm contracts, causing the diaphragm to flatten and drop towards the abdominal cavity, helping to expand the thoracic cavity. The external intercostal muscles contract as well, causing the rib cage to expand, and the rib cage and sternum to move outward, also expanding the thoracic cavity. Expansion of the thoracic cavity also causes the lungs to expand, due to the adhesiveness of the pleural fluid. As a result, the pressure within the lungs drops below that of the atmosphere, causing air to rush into the lungs. In contrast, expiration is a passive process. As the diaphragm and intercostal muscles relax, the lungs and thoracic tissues recoil, and the volume of the lungs decreases. This causes the pressure within the lungs to increase above that of the atmosphere, causing air to leave the lungs.

Exercise:

Problem: What is respiratory rate and how is it controlled?

Solution:

Respiratory rate is defined as the number of breaths taken per minute. Respiratory rate is controlled by the respiratory center, located in the medulla oblongata. Conscious thought can alter the normal respiratory rate through control by skeletal muscle, although one cannot consciously stop the rate altogether. A typical resting respiratory rate is about 14 breaths per minute.

Glossary

alveolar dead space
: air space within alveoli that are unable to participate in gas exchange

anatomical dead space
: air space present in the airway that never reaches the alveoli and therefore never participates in gas exchange

apneustic center
: network of neurons within the pons that stimulate the neurons in the dorsal respiratory group; controls the depth of inspiration

atmospheric pressure
: amount of force that is exerted by gases in the air surrounding any given surface

Boyle's law
: relationship between volume and pressure as described by the formula: $P_1V_1 = P_2V_2$

central chemoreceptor
: one of the specialized receptors that are located in the brain that sense changes in hydrogen ion, oxygen, or carbon dioxide concentrations in the brain

dorsal respiratory group (DRG)

region of the medulla oblongata that stimulates the contraction of the diaphragm and intercostal muscles to induce inspiration

expiration
: (also, exhalation) process that causes the air to leave the lungs

expiratory reserve volume (ERV)
: amount of air that can be forcefully exhaled after a normal tidal exhalation

forced breathing
: (also, hyperpnea) mode of breathing that occurs during exercise or by active thought that requires muscle contraction for both inspiration and expiration

functional residual capacity (FRC)
: sum of ERV and RV, which is the amount of air that remains in the lungs after a tidal expiration

inspiration
: (also, inhalation) process that causes air to enter the lungs

inspiratory capacity (IC)
: sum of the TV and IRV, which is the amount of air that can maximally be inhaled past a tidal expiration

inspiratory reserve volume (IRV)
: amount of air that enters the lungs due to deep inhalation past the tidal volume

intra-alveolar pressure
: (intrapulmonary pressure) pressure of the air within the alveoli

intrapleural pressure
: pressure of the air within the pleural cavity

peripheral chemoreceptor

one of the specialized receptors located in the aortic arch and carotid arteries that sense changes in pH, carbon dioxide, or oxygen blood levels

pneumotaxic center
: network of neurons within the pons that inhibit the activity of the neurons in the dorsal respiratory group; controls rate of breathing

pulmonary ventilation
: exchange of gases between the lungs and the atmosphere; breathing

quiet breathing
: (also, eupnea) mode of breathing that occurs at rest and does not require the cognitive thought of the individual

residual volume (RV)
: amount of air that remains in the lungs after maximum exhalation

respiratory cycle
: one sequence of inspiration and expiration

respiratory rate
: total number of breaths taken each minute

respiratory volume
: varying amounts of air within the lung at a given time

thoracic wall compliance
: ability of the thoracic wall to stretch while under pressure

tidal volume (TV)
: amount of air that normally enters the lungs during quiet breathing

total dead space
: sum of the anatomical dead space and alveolar dead space

total lung capacity (TLC)
: total amount of air that can be held in the lungs; sum of TV, ERV, IRV, and RV

transpulmonary pressure
: pressure difference between the intrapleural and intra-alveolar pressures

ventral respiratory group (VRG)
: region of the medulla oblongata that stimulates the contraction of the accessory muscles involved in respiration to induce forced inspiration and expiration

vital capacity (VC)
: sum of TV, ERV, and IRV, which is all the volumes that participate in gas exchange

Gas Exchange
By the end of this section, you will be able to:

- Compare the composition of atmospheric air and alveolar air
- Describe the mechanisms that drive gas exchange
- Discuss the importance of sufficient ventilation and perfusion, and how the body adapts when they are insufficient
- Discuss the process of external respiration
- Describe the process of internal respiration

The purpose of the respiratory system is to perform gas exchange. Pulmonary ventilation provides air to the alveoli for this gas exchange process. At the respiratory membrane, where the alveolar and capillary walls meet, gases move across the membranes, with oxygen entering the bloodstream and carbon dioxide exiting. It is through this mechanism that blood is oxygenated and carbon dioxide, the waste product of cellular respiration, is removed from the body.

Gas Exchange

In order to understand the mechanisms of gas exchange in the lung, it is important to understand the underlying principles of gases and their behavior. In addition to Boyle's law, several other gas laws help to describe the behavior of gases.

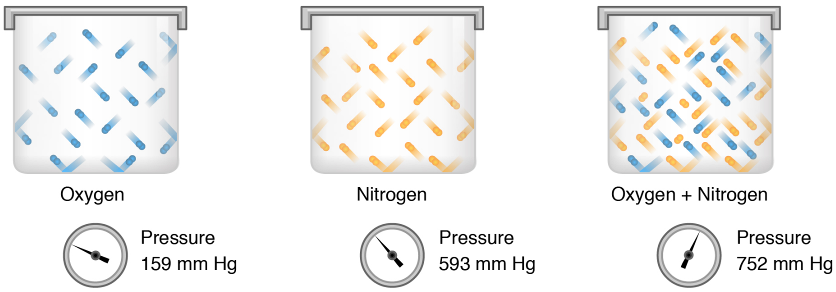
Gas Laws and Air Composition

Gas molecules exert force on the surfaces with which they are in contact; this force is called pressure. In natural systems, gases are normally present as a mixture of different types of molecules. For example, the atmosphere consists of oxygen, nitrogen, carbon dioxide, and other gaseous molecules, and this gaseous mixture exerts a certain pressure referred to as atmospheric pressure ([link]). **Partial pressure** (P_x) is the pressure of a single type of gas in a mixture of gases. For example, in the atmosphere, oxygen exerts a partial pressure, and nitrogen exerts another partial pressure, independent of the partial pressure of oxygen ([link]). **Total pressure** is the sum of all the

partial pressures of a gaseous mixture. **Dalton’s law** describes the behavior of nonreactive gases in a gaseous mixture and states that a specific gas type in a mixture exerts its own pressure; thus, the total pressure exerted by a mixture of gases is the sum of the partial pressures of the gases in the mixture.

Partial Pressures of Atmospheric Gases		
Gas	**Percent of total composition**	**Partial pressure (mm Hg)**
Nitrogen (N_2)	78.6	597.4
Oxygen (O_2)	20.9	158.8
Water (H_2O)	0.4	3.0
Carbon dioxide (CO_2)	0.04	0.3
Others	0.06	0.5
Total composition/total atmospheric pressure	100%	760.0

Partial and Total Pressures of a Gas



Partial pressure is the force exerted by a gas. The sum of the partial pressures of all the gases in a mixture equals the total pressure.

Partial pressure is extremely important in predicting the movement of gases. Recall that gases tend to equalize their pressure in two regions that are connected. A gas will move from an area where its partial pressure is higher to an area where its partial pressure is lower. In addition, the greater the partial pressure difference between the two areas, the more rapid is the movement of gases.

Solubility of Gases in Liquids

Henry's law describes the behavior of gases when they come into contact with a liquid, such as blood. Henry's law states that the concentration of gas in a liquid is directly proportional to the solubility and partial pressure of that gas. The greater the partial pressure of the gas, the greater the number of gas molecules that will dissolve in the liquid. The concentration of the gas in a liquid is also dependent on the solubility of the gas in the liquid. For example, although nitrogen is present in the atmosphere, very little nitrogen dissolves into the blood, because the solubility of nitrogen in blood is very low. The exception to this occurs in scuba divers; the composition of the compressed air that divers breathe causes nitrogen to have a higher partial pressure than normal, causing it to dissolve in the blood in greater amounts than normal. Too much nitrogen in the bloodstream results in a

serious condition that can be fatal if not corrected. Gas molecules establish an equilibrium between those molecules dissolved in liquid and those in air.

The composition of air in the atmosphere and in the alveoli differs. In both cases, the relative concentration of gases is nitrogen > oxygen > water vapor > carbon dioxide. The amount of water vapor present in alveolar air is greater than that in atmospheric air ([link]). Recall that the respiratory system works to humidify incoming air, thereby causing the air present in the alveoli to have a greater amount of water vapor than atmospheric air. In addition, alveolar air contains a greater amount of carbon dioxide and less oxygen than atmospheric air. This is no surprise, as gas exchange removes oxygen from and adds carbon dioxide to alveolar air. Both deep and forced breathing cause the alveolar air composition to be changed more rapidly than during quiet breathing. As a result, the partial pressures of oxygen and carbon dioxide change, affecting the diffusion process that moves these materials across the membrane. This will cause oxygen to enter and carbon dioxide to leave the blood more quickly.

Composition and Partial Pressures of Alveolar Air		
Gas	**Percent of total composition**	**Partial pressure (mm Hg)**
Nitrogen (N_2)	74.9	569
Oxygen (O_2)	13.7	104
Water (H_2O)	6.2	40
Carbon dioxide (CO_2)	5.2	47

Composition and Partial Pressures of Alveolar Air		
Gas	**Percent of total composition**	**Partial pressure (mm Hg)**
Total composition/total alveolar pressure	100%	760.0

Ventilation and Perfusion

Two important aspects of gas exchange in the lung are ventilation and perfusion. **Ventilation** is the movement of air into and out of the lungs, and perfusion is the flow of blood in the pulmonary capillaries. For gas exchange to be efficient, the volumes involved in ventilation and perfusion should be compatible. However, factors such as regional gravity effects on blood, blocked alveolar ducts, or disease can cause ventilation and perfusion to be imbalanced.

The partial pressure of oxygen in alveolar air is about 104 mm Hg, whereas the partial pressure of oxygenated blood in pulmonary veins is about 100 mm Hg. When ventilation is sufficient, oxygen enters the alveoli at a high rate, and the partial pressure of oxygen in the alveoli remains high. In contrast, when ventilation is insufficient, the partial pressure of oxygen in the alveoli drops. Without the large difference in partial pressure between the alveoli and the blood, oxygen does not diffuse efficiently across the respiratory membrane. The body has mechanisms that counteract this problem. In cases when ventilation is not sufficient for an alveolus, the body redirects blood flow to alveoli that are receiving sufficient ventilation. This is achieved by constricting the pulmonary arterioles that serves the dysfunctional alveolus, which redirects blood to other alveoli that have sufficient ventilation. At the same time, the pulmonary arterioles that serve alveoli receiving sufficient ventilation vasodilate, which brings in greater blood flow. Factors such as carbon dioxide, oxygen, and pH levels can all

serve as stimuli for adjusting blood flow in the capillary networks associated with the alveoli.

Ventilation is regulated by the diameter of the airways, whereas perfusion is regulated by the diameter of the blood vessels. The diameter of the bronchioles is sensitive to the partial pressure of carbon dioxide in the alveoli. A greater partial pressure of carbon dioxide in the alveoli causes the bronchioles to increase their diameter as will a decreased level of oxygen in the blood supply, allowing carbon dioxide to be exhaled from the body at a greater rate. As mentioned above, a greater partial pressure of oxygen in the alveoli causes the pulmonary arterioles to dilate, increasing blood flow.

Gas Exchange

Gas exchange occurs at two sites in the body: in the lungs, where oxygen is picked up and carbon dioxide is released at the respiratory membrane, and at the tissues, where oxygen is released and carbon dioxide is picked up. External respiration is the exchange of gases with the external environment, and occurs in the alveoli of the lungs. Internal respiration is the exchange of gases with the internal environment, and occurs in the tissues. The actual exchange of gases occurs due to simple diffusion. Energy is not required to move oxygen or carbon dioxide across membranes. Instead, these gases follow pressure gradients that allow them to diffuse. The anatomy of the lung maximizes the diffusion of gases: The respiratory membrane is highly permeable to gases; the respiratory and blood capillary membranes are very thin; and there is a large surface area throughout the lungs.

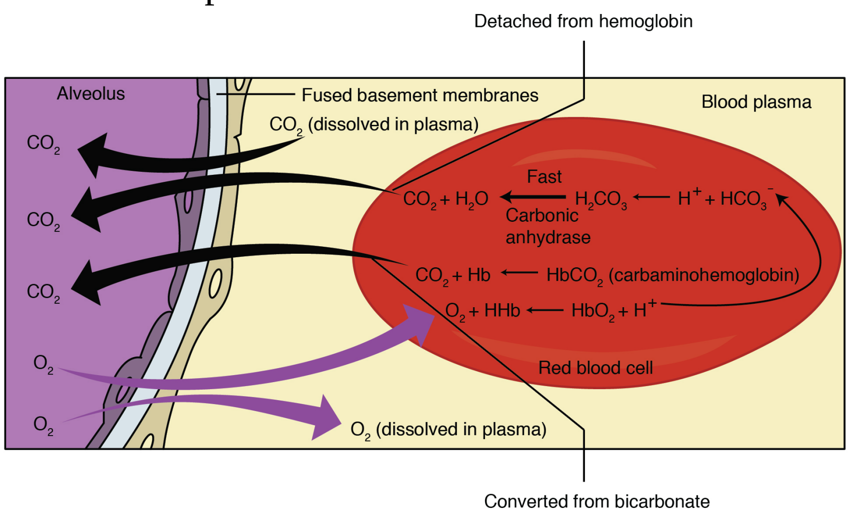
External Respiration

The pulmonary artery carries deoxygenated blood into the lungs from the heart, where it branches and eventually becomes the capillary network composed of pulmonary capillaries. These pulmonary capillaries create the respiratory membrane with the alveoli ([link]). As the blood is pumped through this capillary network, gas exchange occurs. Although a small amount of the oxygen is able to dissolve directly into plasma from the

alveoli, most of the oxygen is picked up by erythrocytes (red blood cells) and binds to a protein called hemoglobin, a process described later in this chapter. Oxygenated hemoglobin is red, causing the overall appearance of bright red oxygenated blood, which returns to the heart through the pulmonary veins. Carbon dioxide is released in the opposite direction of oxygen, from the blood to the alveoli. Some of the carbon dioxide is returned on hemoglobin, but can also be dissolved in plasma or is present as a converted form, also explained in greater detail later in this chapter.

External respiration occurs as a function of partial pressure differences in oxygen and carbon dioxide between the alveoli and the blood in the pulmonary capillaries.

External Respiration



In external respiration, oxygen diffuses across the respiratory membrane from the alveolus to the capillary, whereas carbon dioxide diffuses out of the capillary into the alveolus.

Although the solubility of oxygen in blood is not high, there is a drastic difference in the partial pressure of oxygen in the alveoli versus in the blood of the pulmonary capillaries. This difference is about 64 mm Hg: The partial pressure of oxygen in the alveoli is about 104 mm Hg, whereas its partial pressure in the blood of the capillary is about 40 mm Hg. This large

difference in partial pressure creates a very strong pressure gradient that causes oxygen to rapidly cross the respiratory membrane from the alveoli into the blood.

The partial pressure of carbon dioxide is also different between the alveolar air and the blood of the capillary. However, the partial pressure difference is less than that of oxygen, about 5 mm Hg. The partial pressure of carbon dioxide in the blood of the capillary is about 45 mm Hg, whereas its partial pressure in the alveoli is about 40 mm Hg. However, the solubility of carbon dioxide is much greater than that of oxygen—by a factor of about 20—in both blood and alveolar fluids. As a result, the relative concentrations of oxygen and carbon dioxide that diffuse across the respiratory membrane are similar.

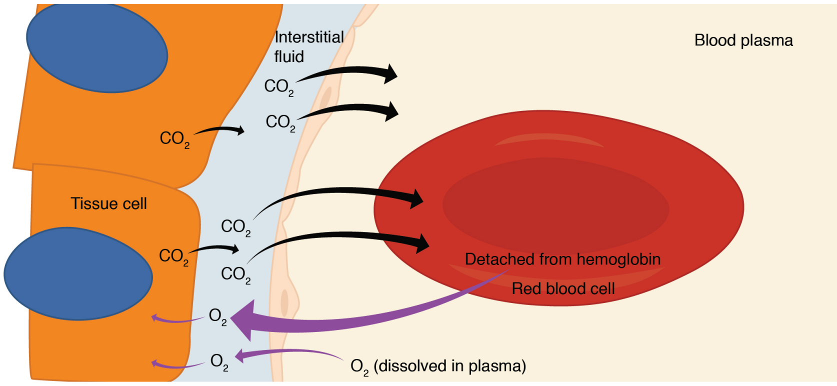
Internal Respiration

Internal respiration is gas exchange that occurs at the level of body tissues ([link]). Similar to external respiration, internal respiration also occurs as simple diffusion due to a partial pressure gradient. However, the partial pressure gradients are opposite of those present at the respiratory membrane. The partial pressure of oxygen in tissues is low, about 40 mm Hg, because oxygen is continuously used for cellular respiration. In contrast, the partial pressure of oxygen in the blood is about 100 mm Hg. This creates a pressure gradient that causes oxygen to dissociate from hemoglobin, diffuse out of the blood, cross the interstitial space, and enter the tissue. Hemoglobin that has little oxygen bound to it loses much of its brightness, so that blood returning to the heart is more burgundy in color.

Considering that cellular respiration continuously produces carbon dioxide, the partial pressure of carbon dioxide is lower in the blood than it is in the tissue, causing carbon dioxide to diffuse out of the tissue, cross the interstitial fluid, and enter the blood. It is then carried back to the lungs either bound to hemoglobin, dissolved in plasma, or in a converted form. By the time blood returns to the heart, the partial pressure of oxygen has returned to about 40 mm Hg, and the partial pressure of carbon dioxide has

returned to about 45 mm Hg. The blood is then pumped back to the lungs to be oxygenated once again during external respiration.

Internal Respiration



Oxygen diffuses out of the capillary and into cells, whereas carbon dioxide diffuses out of cells and into the capillary.

Note:

Everyday Connection

Hyperbaric Chamber Treatment

A type of device used in some areas of medicine that exploits the behavior of gases is hyperbaric chamber treatment. A hyperbaric chamber is a unit that can be sealed and expose a patient to either 100 percent oxygen with increased pressure or a mixture of gases that includes a higher concentration of oxygen than normal atmospheric air, also at a higher partial pressure than the atmosphere. There are two major types of chambers: monoplace and multiplace. Monoplace chambers are typically for one patient, and the staff tending to the patient observes the patient from outside of the chamber ([link]). Some facilities have special monoplace hyperbaric chambers that allow multiple patients to be treated at once, usually in a sitting or reclining position, to help ease feelings of isolation or claustrophobia. Multiplace chambers are large enough for multiple patients to be treated at one time, and the staff attending these

patients is present inside the chamber. In a multiplace chamber, patients are often treated with air via a mask or hood, and the chamber is pressurized.

Hyperbaric Chamber

(credit: “komunews”/flickr.com)

Hyperbaric chamber treatment is based on the behavior of gases. As you recall, gases move from a region of higher partial pressure to a region of lower partial pressure. In a hyperbaric chamber, the atmospheric pressure is increased, causing a greater amount of oxygen than normal to diffuse into the bloodstream of the patient. Hyperbaric chamber therapy is used to treat a variety of medical problems, such as wound and graft healing, anaerobic bacterial infections, and carbon monoxide poisoning. Exposure to and poisoning by carbon monoxide is difficult to reverse, because hemoglobin’s affinity for carbon monoxide is much stronger than its affinity for oxygen, causing carbon monoxide to replace oxygen in the blood. Hyperbaric chamber therapy can treat carbon monoxide poisoning, because the increased atmospheric pressure causes more oxygen to diffuse into the bloodstream. At this increased pressure and increased concentration of oxygen, carbon monoxide is displaced from hemoglobin. Another example is the treatment of anaerobic bacterial infections, which are created by bacteria that cannot or prefer not to live in the presence of oxygen. An increase in blood and tissue levels of oxygen helps to kill the

anaerobic bacteria that are responsible for the infection, as oxygen is toxic to anaerobic bacteria. For wounds and grafts, the chamber stimulates the healing process by increasing energy production needed for repair. Increasing oxygen transport allows cells to ramp up cellular respiration and thus ATP production, the energy needed to build new structures.

Chapter Review

The behavior of gases can be explained by the principles of Dalton's law and Henry's law, both of which describe aspects of gas exchange. Dalton's law states that each specific gas in a mixture of gases exerts force (its partial pressure) independently of the other gases in the mixture. Henry's law states that the amount of a specific gas that dissolves in a liquid is a function of its partial pressure. The greater the partial pressure of a gas, the more of that gas will dissolve in a liquid, as the gas moves toward equilibrium. Gas molecules move down a pressure gradient; in other words, gas moves from a region of high pressure to a region of low pressure. The partial pressure of oxygen is high in the alveoli and low in the blood of the pulmonary capillaries. As a result, oxygen diffuses across the respiratory membrane from the alveoli into the blood. In contrast, the partial pressure of carbon dioxide is high in the pulmonary capillaries and low in the alveoli. Therefore, carbon dioxide diffuses across the respiratory membrane from the blood into the alveoli. The amount of oxygen and carbon dioxide that diffuses across the respiratory membrane is similar.

Ventilation is the process that moves air into and out of the alveoli, and perfusion affects the flow of blood in the capillaries. Both are important in gas exchange, as ventilation must be sufficient to create a high partial pressure of oxygen in the alveoli. If ventilation is insufficient and the partial pressure of oxygen drops in the alveolar air, the capillary is constricted and blood flow is redirected to alveoli with sufficient ventilation. External respiration refers to gas exchange that occurs in the alveoli, whereas internal respiration refers to gas exchange that occurs in the tissue. Both are driven by partial pressure differences.

Review Questions

Exercise:

Problem:

Gas moves from an area of _________ partial pressure to an area of _________ partial pressure.

a. low; high
b. low; low
c. high; high
d. high; low

Solution:

D

Exercise:

Problem:

When ventilation is not sufficient, which of the following occurs?

a. The capillary constricts.
b. The capillary dilates.
c. The partial pressure of oxygen in the affected alveolus increases.
d. The bronchioles dilate.

Solution:

A

Exercise:

Problem:

Gas exchange that occurs at the level of the tissues is called _________.

a. external respiration
b. interpulmonary respiration
c. internal respiration
d. pulmonary ventilation

Solution:

C

Exercise:

Problem:

The partial pressure of carbon dioxide is 45 mm Hg in the blood and 40 mm Hg in the alveoli. What happens to the carbon dioxide?

a. It diffuses into the blood.
b. It diffuses into the alveoli.
c. The gradient is too small for carbon dioxide to diffuse.
d. It decomposes into carbon and oxygen.

Solution:

B

Critical Thinking Questions

Exercise:

Problem: Compare and contrast Dalton’s law and Henry’s law.

Solution:

Both Dalton’s and Henry’s laws describe the behavior of gases. Dalton’s law states that any gas in a mixture of gases exerts force as if

it were not in a mixture. Henry’s law states that gas molecules dissolve in a liquid proportional to their partial pressure.

Exercise:

Problem:

A smoker develops damage to several alveoli that then can no longer function. How does this affect gas exchange?

Solution:

The damaged alveoli will have insufficient ventilation, causing the partial pressure of oxygen in the alveoli to decrease. As a result, the pulmonary capillaries serving these alveoli will constrict, redirecting blood flow to other alveoli that are receiving sufficient ventilation.

Glossary

Dalton’s law
: statement of the principle that a specific gas type in a mixture exerts its own pressure, as if that specific gas type was not part of a mixture of gases

external respiration
: gas exchange that occurs in the alveoli

Henry’s law
: statement of the principle that the concentration of gas in a liquid is directly proportional to the solubility and partial pressure of that gas

internal respiration
: gas exchange that occurs at the level of body tissues

partial pressure
: force exerted by each gas in a mixture of gases

total pressure

sum of all the partial pressures of a gaseous mixture

ventilation

movement of air into and out of the lungs; consists of inspiration and expiration

Transport of Gases
By the end of this section, you will be able to:

- Describe the principles of oxygen transport
- Describe the structure of hemoglobin
- Compare and contrast fetal and adult hemoglobin
- Describe the principles of carbon dioxide transport

The other major activity in the lungs is the process of respiration, the process of gas exchange. The function of respiration is to provide oxygen for use by body cells during cellular respiration and to eliminate carbon dioxide, a waste product of cellular respiration, from the body. In order for the exchange of oxygen and carbon dioxide to occur, both gases must be transported between the external and internal respiration sites. Although carbon dioxide is more soluble than oxygen in blood, both gases require a specialized transport system for the majority of the gas molecules to be moved between the lungs and other tissues.

Oxygen Transport in the Blood

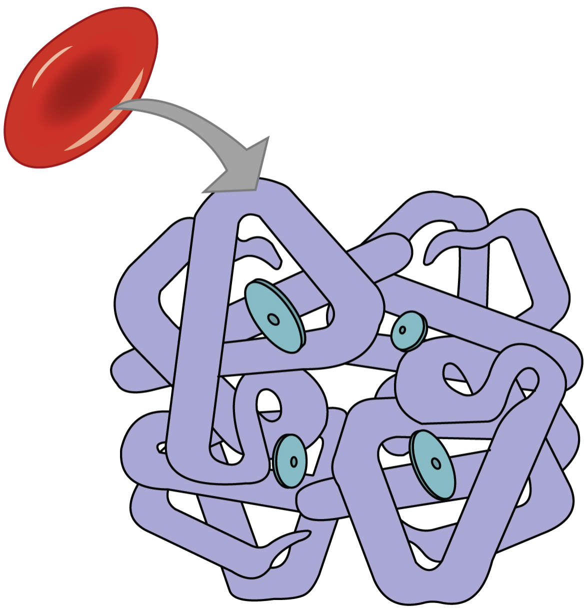
Even though oxygen is transported via the blood, you may recall that oxygen is not very soluble in liquids. A small amount of oxygen does dissolve in the blood and is transported in the bloodstream, but it is only about 1.5% of the total amount. The majority of oxygen molecules are carried from the lungs to the body's tissues by a specialized transport system, which relies on the erythrocyte—the red blood cell. Erythrocytes contain a metalloprotein, hemoglobin, which serves to bind oxygen molecules to the erythrocyte ([link]). Heme is the portion of hemoglobin that contains iron, and it is heme that binds oxygen. One hemoglobin molecule contains iron-containing Heme molecules, and because of this, each hemoglobin molecule is capable of carrying up to four molecules of oxygen. As oxygen diffuses across the respiratory membrane from the alveolus to the capillary, it also diffuses into the red blood cell and is bound by hemoglobin. The following reversible chemical reaction describes the production of the final product, **oxyhemoglobin** ($Hb–O_2$), which is formed when oxygen binds to hemoglobin. Oxyhemoglobin is a bright red-colored molecule that contributes to the bright red color of oxygenated blood.

Equation:

$$Hb + O_2 \leftrightarrow Hb - O_2$$

In this formula, Hb represents reduced hemoglobin, that is, hemoglobin that does not have oxygen bound to it. There are multiple factors involved in how readily heme binds to and dissociates from oxygen, which will be discussed in the subsequent sections.

Erythrocyte and Hemoglobin



Hemoglobin consists of four subunits, each of which contains one molecule of iron.

Function of Hemoglobin

Hemoglobin is composed of subunits, a protein structure that is referred to as a quaternary structure. Each of the four subunits that make up hemoglobin is arranged in a ring-like fashion, with an iron atom covalently bound to the heme in the center of each subunit. Binding of the first oxygen

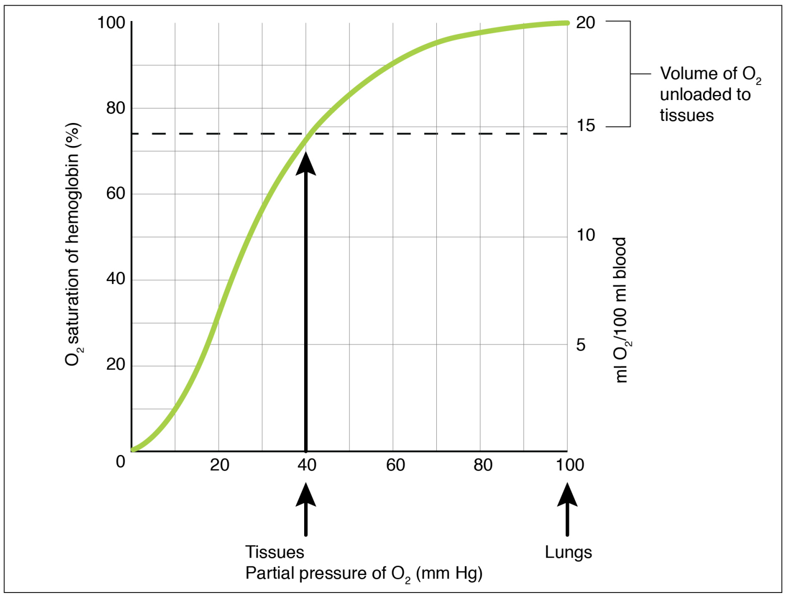
molecule causes a conformational change in hemoglobin that allows the second molecule of oxygen to bind more readily. As each molecule of oxygen is bound, it further facilitates the binding of the next molecule, until all four heme sites are occupied by oxygen. The opposite occurs as well: After the first oxygen molecule dissociates and is “dropped off” at the tissues, the next oxygen molecule dissociates more readily. When all four heme sites are occupied, the hemoglobin is said to be saturated. When one to three heme sites are occupied, the hemoglobin is said to be partially saturated. Therefore, when considering the blood as a whole, the percent of the available heme units that are bound to oxygen at a given time is called hemoglobin saturation. Hemoglobin saturation of 100 percent means that every heme unit in all of the erythrocytes of the body is bound to oxygen. In a healthy individual with normal hemoglobin levels, hemoglobin saturation generally ranges from 95 percent to 99 percent.

Oxygen Dissociation from Hemoglobin

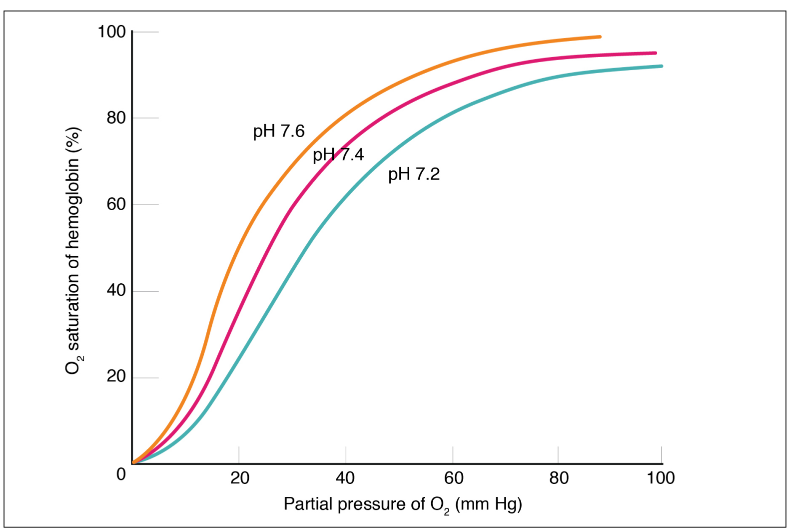
Partial pressure is an important aspect of the binding of oxygen to and disassociation from heme. An **oxygen–hemoglobin dissociation curve** is a graph that describes the relationship of partial pressure to the binding of oxygen to heme and its subsequent dissociation from heme ([link]). Remember that gases travel from an area of higher partial pressure to an area of lower partial pressure. In addition, the affinity of an oxygen molecule for heme increases as more oxygen molecules are bound. Therefore, in the oxygen–hemoglobin saturation curve, as the partial pressure of oxygen increases, a proportionately greater number of oxygen molecules are bound by heme. Not surprisingly, the oxygen–hemoglobin saturation/dissociation curve also shows that the lower the partial pressure of oxygen, the fewer oxygen molecules are bound to heme. As a result, the partial pressure of oxygen plays a major role in determining the degree of binding of oxygen to heme at the site of the respiratory membrane, as well as the degree of dissociation of oxygen from heme at the site of body tissues.

Oxygen-Hemoglobin Dissociation and Effects of pH and Temperature

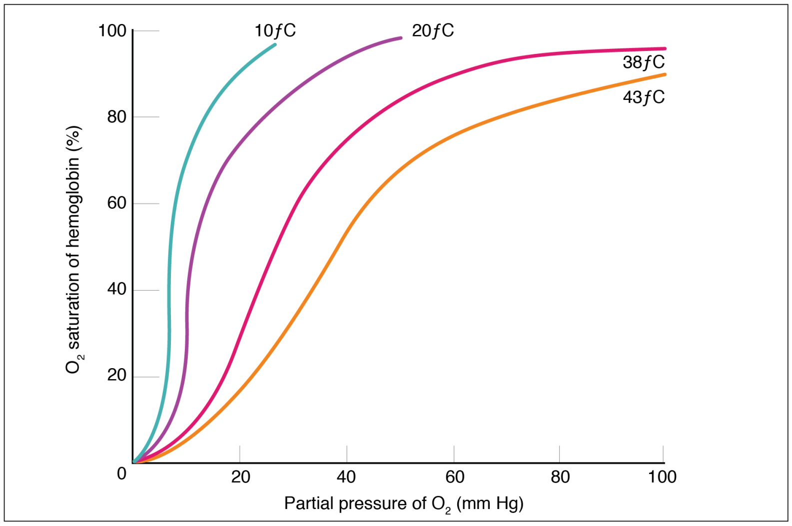
These three graphs show (a) the relationship between the partial pressure of oxygen and hemoglobin saturation, (b) the effect of pH on the oxygen–hemoglobin dissociation curve, and (c) the effect of temperature on the oxygen–hemoglobin dissociation curve.



(a) Partial pressure of oxygen and hemoglobin saturation



(b) Effect of pH



(c) Effect of temperature

The mechanisms behind the oxygen–hemoglobin saturation/dissociation curve also serve as automatic control mechanisms that regulate how much oxygen is delivered to different tissues throughout the body. This is important because some tissues have a higher metabolic rate than others. Highly active tissues, such as muscle, rapidly use oxygen to produce ATP, lowering the partial pressure of oxygen in the tissue to about 20 mm Hg. The partial pressure of oxygen inside capillaries is about 100 mm Hg, so the difference between the two becomes quite high, about 80 mm Hg. As a result, a greater number of oxygen molecules dissociate from hemoglobin and enter the tissues. The reverse is true of tissues, such as adipose (body fat), which have lower metabolic rates. Because less oxygen is used by these cells, the partial pressure of oxygen within such tissues remains relatively high, resulting in fewer oxygen molecules dissociating from hemoglobin and entering the tissue interstitial fluid. Although venous blood is said to be deoxygenated, some oxygen is still bound to hemoglobin in its red blood cells. This provides an oxygen reserve that can be used when tissues suddenly demand more oxygen.

Factors other than partial pressure also affect the oxygen–hemoglobin saturation/dissociation curve. For example, a higher temperature promotes hemoglobin and oxygen to dissociate faster, whereas a lower temperature inhibits dissociation (see [link]**, middle**). However, the human body tightly regulates temperature, so this factor may not affect gas exchange throughout the body. The exception to this is in highly active tissues, which

may release a larger amount of energy than is given off as heat. As a result, oxygen readily dissociates from hemoglobin, which is a mechanism that helps to provide active tissues with more oxygen.

Certain hormones, such as androgens, epinephrine, thyroid hormones, and growth hormone, can affect the oxygen–hemoglobin saturation/disassociation curve by stimulating the production of a compound called 2,3-bisphosphoglycerate (BPG) by erythrocytes. BPG is a byproduct of glycolysis. Because erythrocytes do not contain mitochondria, glycolysis is the sole method by which these cells produce ATP. BPG promotes the disassociation of oxygen from hemoglobin. Therefore, the greater the concentration of BPG, the more readily oxygen dissociates from hemoglobin, despite its partial pressure.

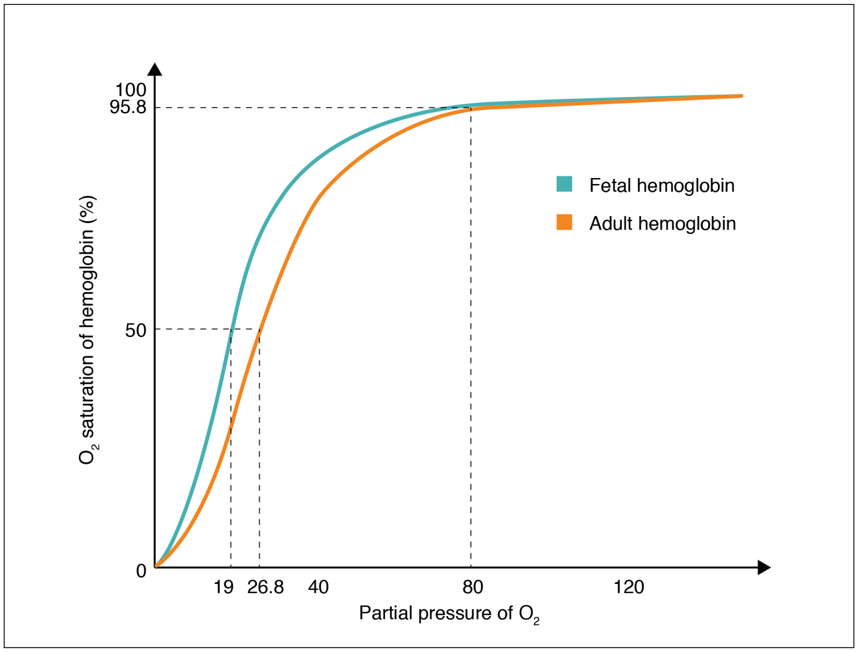
The pH of the blood is another factor that influences the oxygen–hemoglobin saturation/dissociation curve (see [link]). The **Bohr effect** is a phenomenon that arises from the relationship between pH and oxygen's affinity for hemoglobin: A lower, more acidic pH promotes oxygen dissociation from hemoglobin. In contrast, a higher, or more basic, pH inhibits oxygen dissociation from hemoglobin. The greater the amount of carbon dioxide in the blood, the more molecules that must be converted, which in turn generates hydrogen ions and thus lowers blood pH. Furthermore, blood pH may become more acidic when certain byproducts of cell metabolism, such as lactic acid, carbonic acid, and carbon dioxide, are released into the bloodstream.

Hemoglobin of the Fetus

The fetus has its own circulation with its own erythrocytes; however, it is dependent on the mother for oxygen. Blood is supplied to the fetus by way of the umbilical cord, which is connected to the placenta and separated from maternal blood by the chorion. The mechanism of gas exchange at the chorion is similar to gas exchange at the respiratory membrane. However, the partial pressure of oxygen is lower in the maternal blood in the placenta, at about 35 to 50 mm Hg, than it is in maternal arterial blood. The difference in partial pressures between maternal and fetal blood is not large,

as the partial pressure of oxygen in fetal blood at the placenta is about 20 mm Hg. Therefore, there is not as much diffusion of oxygen into the fetal blood supply. The fetus' hemoglobin overcomes this problem by having a greater affinity for oxygen than maternal hemoglobin ([link]). Both fetal and adult hemoglobin have four subunits, but two of the subunits of fetal hemoglobin have a different structure that causes fetal hemoglobin to have a greater affinity for oxygen than does adult hemoglobin.

Oxygen-Hemoglobin Dissociation Curves in Fetus and Adult

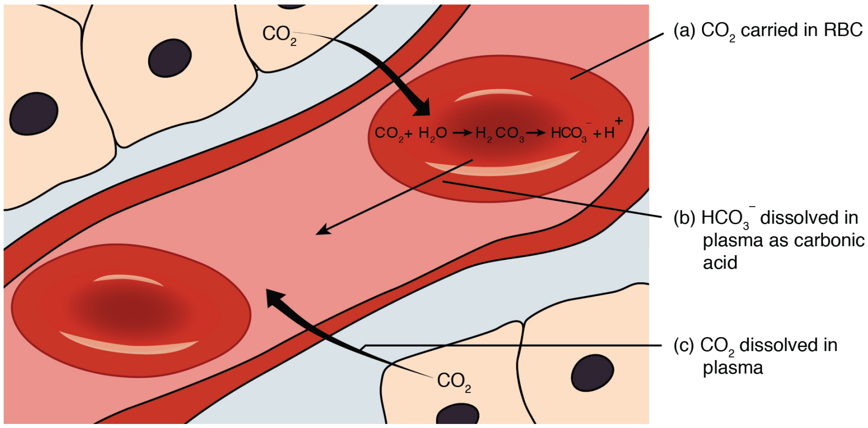


Fetal hemoglobin has a greater affinity for oxygen than does adult hemoglobin.

Carbon Dioxide Transport in the Blood

Carbon dioxide is transported by three major mechanisms. The first mechanism of carbon dioxide transport is by blood plasma, as some carbon dioxide molecules dissolve in the blood. The second mechanism is transport in the form of bicarbonate (HCO_3^-), which also dissolves in plasma. The third mechanism of carbon dioxide transport is similar to the transport of oxygen by erythrocytes ([link]).

Carbon Dioxide Transport



Carbon dioxide is transported by three different methods: (a) in erythrocytes; (b) after forming carbonic acid (H_2CO_3), which is dissolved in plasma; (c) and in plasma.

Dissolved Carbon Dioxide

Although carbon dioxide is not considered to be highly soluble in blood, a small fraction—about 7 to 10 percent—of the carbon dioxide that diffuses into the blood from the tissues dissolves in plasma. The dissolved carbon dioxide then travels in the bloodstream and when the blood reaches the pulmonary capillaries, the dissolved carbon dioxide diffuses across the respiratory membrane into the alveoli, where it is then exhaled during pulmonary ventilation.

Bicarbonate Buffer

A large fraction—about 70 percent—of the carbon dioxide molecules that diffuse into the blood is transported to the lungs as bicarbonate. Most bicarbonate is produced in erythrocytes after carbon dioxide diffuses into the capillaries, and subsequently into red blood cells. **Carbonic anhydrase**

(CA) causes carbon dioxide and water to form carbonic acid (H_2CO_3), which dissociates into two ions: bicarbonate (HCO_3^-) and hydrogen (H^+). The following formula depicts this reaction:

Equation:

$$CO_2 + H_2O \overset{CA}{\leftrightarrow} H_2CO_3 \leftrightarrow H^+ + HCO_{3-}$$

Bicarbonate tends to build up in the erythrocytes, so that there is a greater concentration of bicarbonate in the erythrocytes than in the surrounding blood plasma. As a result, some of the bicarbonate will leave the erythrocytes and move down its concentration gradient into the plasma in exchange for chloride (Cl^-) ions. This phenomenon is referred to as the **chloride shift** and occurs because by exchanging one negative ion for another negative ion, neither the electrical charge of the erythrocytes nor that of the blood is altered.

At the pulmonary capillaries, the chemical reaction that produced bicarbonate (shown above) is reversed, and carbon dioxide and water are the products. Much of the bicarbonate in the plasma re-enters the erythrocytes in exchange for chloride ions. Hydrogen ions and bicarbonate ions join to form carbonic acid, which is converted into carbon dioxide and water by carbonic anhydrase. Carbon dioxide diffuses out of the erythrocytes and into the plasma, where it can further diffuse across the respiratory membrane into the alveoli to be exhaled during pulmonary ventilation.

Carbaminohemoglobin

About 20 percent of carbon dioxide is bound by hemoglobin and is transported to the lungs. Carbon dioxide does not bind to iron as oxygen does; instead, carbon dioxide binds amino acid moieties on the globin portions of hemoglobin to form **carbaminohemoglobin**, which forms when hemoglobin and carbon dioxide bind. When hemoglobin is not transporting oxygen, it tends to have a bluish-purple tone to it, creating the darker

maroon color typical of deoxygenated blood. The following formula depicts this reversible reaction:

Equation:

$$CO_2 + Hb \leftrightarrow HbCO_2$$

Similar to the transport of oxygen by heme, the binding and dissociation of carbon dioxide to and from hemoglobin is dependent on the partial pressure of carbon dioxide. Because carbon dioxide is released from the lungs, blood that leaves the lungs and reaches body tissues has a lower partial pressure of carbon dioxide than is found in the tissues. As a result, carbon dioxide leaves the tissues because of its higher partial pressure, enters the blood, and then moves into red blood cells, binding to hemoglobin. In contrast, in the pulmonary capillaries, the partial pressure of carbon dioxide is high compared to within the alveoli. As a result, carbon dioxide dissociates readily from hemoglobin and diffuses across the respiratory membrane into the air.

In addition to the partial pressure of carbon dioxide, the oxygen saturation of hemoglobin and the partial pressure of oxygen in the blood also influence the affinity of hemoglobin for carbon dioxide. The **Haldane effect** is a phenomenon that arises from the relationship between the partial pressure of oxygen and the affinity of hemoglobin for carbon dioxide. Hemoglobin that is saturated with oxygen does not readily bind carbon dioxide. However, when oxygen is not bound to heme and the partial pressure of oxygen is low, hemoglobin readily binds to carbon dioxide.

Note:

Watch this video to see the transport of oxygen from the lungs to the tissues. Why is oxygenated blood bright red, whereas deoxygenated blood tends to be more of a purple color?

Chapter Review

Oxygen is primarily transported through the blood by erythrocytes. These cells contain a metalloprotein called hemoglobin, which is composed of four subunits with a ring-like structure. Each subunit contains one atom of iron bound to a molecule of heme. Heme binds oxygen so that each hemoglobin molecule can bind up to four oxygen molecules. When all of the heme units in the blood are bound to oxygen, hemoglobin is considered to be saturated. Hemoglobin is partially saturated when only some heme units are bound to oxygen. An oxygen–hemoglobin saturation/dissociation curve is a common way to depict the relationship of how easily oxygen binds to or dissociates from hemoglobin as a function of the partial pressure of oxygen. As the partial pressure of oxygen increases, the more readily hemoglobin binds to oxygen. At the same time, once one molecule of oxygen is bound by hemoglobin, additional oxygen molecules more readily bind to hemoglobin. Other factors such as temperature, pH, the partial pressure of carbon dioxide, and the concentration of 2,3-bisphosphoglycerate can enhance or inhibit the binding of hemoglobin and oxygen as well. Fetal hemoglobin has a different structure than adult hemoglobin, which results in fetal hemoglobin having a greater affinity for oxygen than adult hemoglobin.

Carbon dioxide is transported in blood by three different mechanisms: as dissolved carbon dioxide, as bicarbonate, or as carbaminohemoglobin. A small portion of carbon dioxide remains. The largest amount of transported carbon dioxide is as bicarbonate, formed in erythrocytes. For this conversion, carbon dioxide is combined with water with the aid of an enzyme called carbonic anhydrase. This combination forms carbonic acid, which spontaneously dissociates into bicarbonate and hydrogen ions. As bicarbonate builds up in erythrocytes, it is moved across the membrane into the plasma in exchange for chloride ions by a mechanism called the

chloride shift. At the pulmonary capillaries, bicarbonate re-enters erythrocytes in exchange for chloride ions, and the reaction with carbonic anhydrase is reversed, recreating carbon dioxide and water. Carbon dioxide then diffuses out of the erythrocyte and across the respiratory membrane into the air. An intermediate amount of carbon dioxide binds directly to hemoglobin to form carbaminohemoglobin. The partial pressures of carbon dioxide and oxygen, as well as the oxygen saturation of hemoglobin, influence how readily hemoglobin binds carbon dioxide. The less saturated hemoglobin is and the lower the partial pressure of oxygen in the blood is, the more readily hemoglobin binds to carbon dioxide. This is an example of the Haldane effect.

Interactive Link Questions

Exercise:

Problem:

Watch this video to see the transport of oxygen from the lungs to the tissues. Why is oxygenated blood bright red, whereas deoxygenated blood tends to be more of a purple color?

Solution:

When oxygen binds to the hemoglobin molecule, oxyhemoglobin is created, which has a red color to it. Hemoglobin that is not bound to oxygen tends to be more of a blue–purple color. Oxygenated blood traveling through the systemic arteries has large amounts of oxyhemoglobin. As blood passes through the tissues, much of the oxygen is released into systemic capillaries. The deoxygenated blood returning through the systemic veins, therefore, contains much smaller amounts of oxyhemoglobin. The more oxyhemoglobin that is present in the blood, the redder the fluid will be. As a result, oxygenated blood will be much redder in color than deoxygenated blood.

Review Questions

Exercise:

Problem:

Oxyhemoglobin forms by a chemical reaction between which of the following?

a. hemoglobin and carbon dioxide
b. carbonic anhydrase and carbon dioxide
c. hemoglobin and oxygen
d. carbonic anhydrase and oxygen

Solution:

C

Exercise:

Problem:

Which of the following factors play a role in the oxygen–hemoglobin saturation/dissociation curve?

a. temperature
b. pH
c. BPG
d. all of the above

Solution:

D

Exercise:

Problem: Which of the following occurs during the chloride shift?

a. Chloride is removed from the erythrocyte.
b. Chloride is exchanged for bicarbonate.

c. Bicarbonate is removed from the erythrocyte.
d. Bicarbonate is removed from the blood.

Solution:

B

Exercise:

Problem:

A low partial pressure of oxygen promotes hemoglobin binding to carbon dioxide. This is an example of the _________.

a. Haldane effect
b. Bohr effect
c. Dalton's law
d. Henry's law

Solution:

A

Critical Thinking Questions

Exercise:

Problem:

Compare and contrast adult hemoglobin and fetal hemoglobin.

Solution:

Both adult and fetal hemoglobin transport oxygen via iron molecules. However, fetal hemoglobin has about a 20-fold greater affinity for oxygen than does adult hemoglobin. This is due to a difference in

structure; fetal hemoglobin has two subunits that have a slightly different structure than the subunits of adult hemoglobin.

Exercise:

Problem:

Describe the relationship between the partial pressure of oxygen and the binding of oxygen to hemoglobin.

Solution:

The relationship between the partial pressure of oxygen and the binding of hemoglobin to oxygen is described by the oxygen–hemoglobin saturation/dissociation curve. As the partial pressure of oxygen increases, the number of oxygen molecules bound by hemoglobin increases, thereby increasing the saturation of hemoglobin.

Exercise:

Problem:

Describe three ways in which carbon dioxide can be transported.

Solution:

Carbon dioxide can be transported by three mechanisms: dissolved in plasma, as bicarbonate, or as carbaminohemoglobin. Dissolved in plasma, carbon dioxide molecules simply diffuse into the blood from the tissues. Bicarbonate is created by a chemical reaction that occurs mostly in erythrocytes, joining carbon dioxide and water by carbonic anhydrase, producing carbonic acid, which breaks down into bicarbonate and hydrogen ions. Carbaminohemoglobin is the bound form of hemoglobin and carbon dioxide.

Glossary

Bohr effect

relationship between blood pH and oxygen dissociation from hemoglobin

carbaminohemoglobin
: bound form of hemoglobin and carbon dioxide

carbonic anhydrase (CA)
: enzyme that catalyzes the reaction that causes carbon dioxide and water to form carbonic acid

chloride shift
: facilitated diffusion that exchanges bicarbonate (HCO_3^-) with chloride (Cl^-) ions

Haldane effect
: relationship between the partial pressure of oxygen and the affinity of hemoglobin for carbon dioxide

oxyhemoglobin
: ($Hb–O_2$) bound form of hemoglobin and oxygen

oxygen–hemoglobin dissociation curve
: graph that describes the relationship of partial pressure to the binding and disassociation of oxygen to and from heme

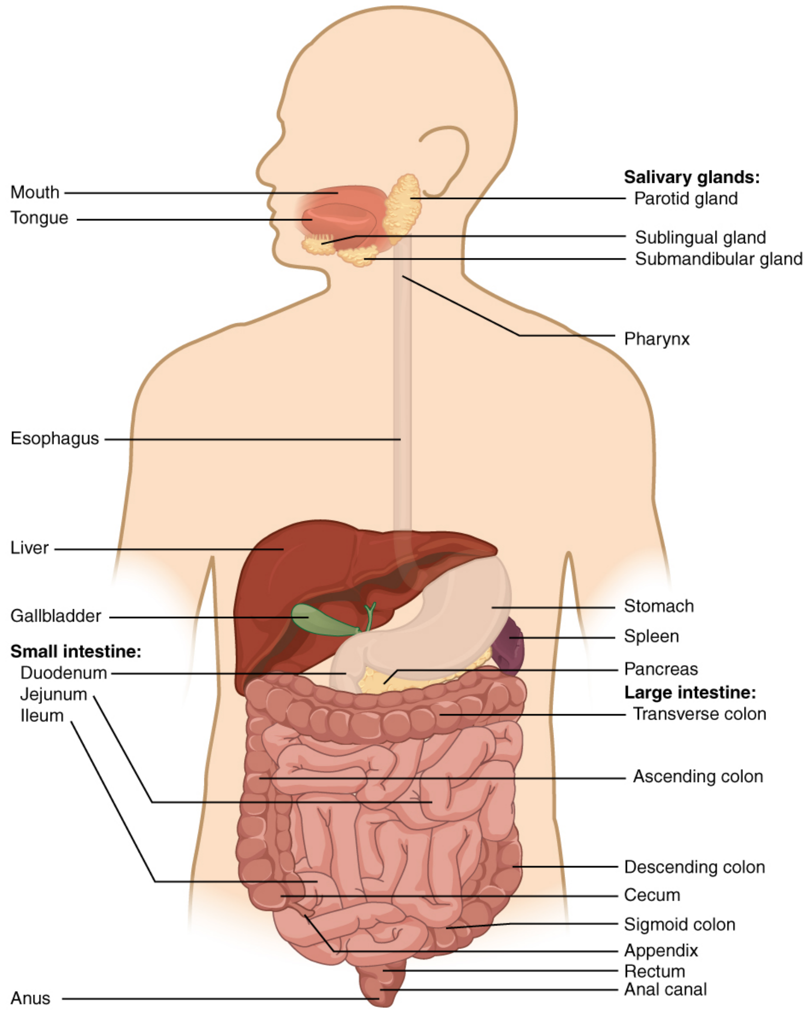
Overview of the Digestive System

By the end of this section, you will be able to:

- Identify the organs of the alimentary canal from proximal to distal, and briefly state their function
- Identify the accessory digestive organs and briefly state their function
- Describe the four fundamental tissue layers of the alimentary canal
- Contrast the contributions of the enteric and autonomic nervous systems to digestive system functioning
- Explain how the peritoneum anchors the digestive organs

The function of the digestive system is to break down the foods you eat, release their nutrients, and absorb those nutrients into the body. Although the small intestine is the workhorse of the system, where the majority of digestion occurs, and where most of the released nutrients are absorbed into the blood or lymph, each of the digestive system organs makes a vital contribution to this process ([link]).

Components of the Digestive System



All digestive organs play integral roles in the life-sustaining process of digestion.

As is the case with all body systems, the digestive system does not work in isolation; it functions cooperatively with the other systems of the body. Consider for example, the interrelationship between the digestive and cardiovascular systems. Arteries supply the digestive organs with oxygen and processed nutrients, and veins drain the digestive tract. These intestinal veins, constituting the hepatic portal system, are unique; they do not return blood directly to the heart. Rather, this blood is diverted to the liver where its nutrients are off-loaded for processing before blood completes its circuit back to the heart. At the same time, the digestive system provides nutrients

to the heart muscle and vascular tissue to support their functioning. The interrelationship of the digestive and endocrine systems is also critical. Hormones secreted by several endocrine glands, as well as endocrine cells of the pancreas, the stomach, and the small intestine, contribute to the control of digestion and nutrient metabolism. In turn, the digestive system provides the nutrients to fuel endocrine function. [link] gives a quick glimpse at how these other systems contribute to the functioning of the digestive system.

Contribution of Other Body Systems to the Digestive System	
Body system	**Benefits received by the digestive system**
Cardiovascular	Blood supplies digestive organs with oxygen and processed nutrients
Endocrine	Endocrine hormones help regulate secretion in digestive glands and accessory organs
Integumentary	Skin helps protect digestive organs and synthesizes vitamin D for calcium absorption
Lymphatic	Mucosa-associated lymphoid tissue and other lymphatic tissue defend against entry of pathogens; lacteals absorb lipids; and lymphatic vessels transport lipids to bloodstream
Muscular	Skeletal muscles support and protect abdominal organs

Contribution of Other Body Systems to the Digestive System	
Body system	**Benefits received by the digestive system**
Nervous	Sensory and motor neurons help regulate secretions and muscle contractions in the digestive tract
Respiratory	Respiratory organs provide oxygen and remove carbon dioxide
Skeletal	Bones help protect and support digestive organs
Urinary	Kidneys convert vitamin D into its active form, allowing calcium absorption in the small intestine

Digestive System Organs

The easiest way to understand the digestive system is to divide its organs into two main categories. The first group is the organs that make up the alimentary canal. Accessory digestive organs comprise the second group and are critical for orchestrating the breakdown of food and the assimilation of its nutrients into the body. Accessory digestive organs, despite their name, are critical to the function of the digestive system.

Alimentary Canal Organs

Also called the gastrointestinal (GI) tract or gut, the **alimentary canal** (aliment- = “to nourish”) is a one-way tube about 7.62 meters (25 feet) in length during life and closer to 10.67 meters (35 feet) in length when measured after death, once smooth muscle tone is lost. The main function of the organs of the alimentary canal is to nourish the body. This tube begins at the mouth and terminates at the anus. Between those two points, the canal is modified as the pharynx, esophagus, stomach, and small and

large intestines to fit the functional needs of the body. Both the mouth and anus are open to the external environment; thus, food and wastes within the alimentary canal are technically considered to be outside the body. Only through the process of absorption do the nutrients in food enter into and nourish the body's "inner space."

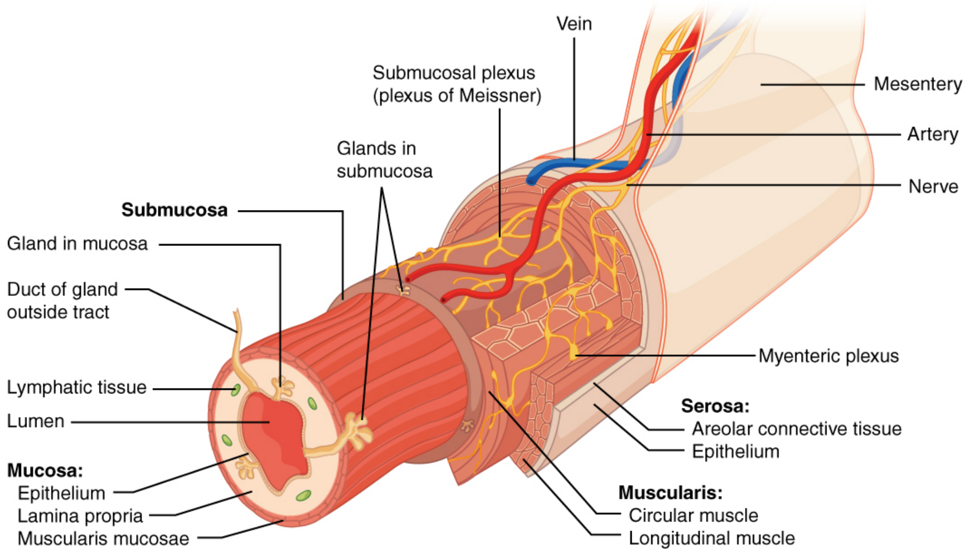
Accessory Structures

Each **accessory digestive organ** aids in the breakdown of food ([link]). Within the mouth, the teeth and tongue begin mechanical digestion, whereas the salivary glands begin chemical digestion. Once food products enter the small intestine, the gallbladder, liver, and pancreas release secretions—such as bile and enzymes—essential for digestion to continue. Together, these are called accessory organs because they sprout from the lining cells of the developing gut (mucosa) and augment its function; indeed, you could not live without their vital contributions, and many significant diseases result from their malfunction. Even after development is complete, they maintain a connection to the gut by way of ducts.

Histology of the Alimentary Canal

Throughout its length, the alimentary tract is composed of the same four tissue layers; the details of their structural arrangements vary to fit their specific functions. Starting from the lumen and moving outwards, these layers are the mucosa, submucosa, muscularis, and serosa, which is continuous with the mesentery (see [link]).

Layers of the Alimentary Canal



The wall of the alimentary canal has four basic tissue layers: the mucosa, submucosa, muscularis, and serosa.

The **mucosa** is referred to as a mucous membrane, because mucus production is a characteristic feature of gut epithelium. The membrane consists of epithelium, which is in direct contact with ingested food, and the lamina propria, a layer of connective tissue analogous to the dermis. In addition, the mucosa has a thin, smooth muscle layer, called the muscularis mucosa (not to be confused with the muscularis layer, described below).

Epithelium—In the mouth, pharynx, esophagus, and anal canal, the epithelium is primarily a non-keratinized, stratified squamous epithelium. In the stomach and intestines, it is a simple columnar epithelium. Notice that the epithelium is in direct contact with the lumen, the space inside the alimentary canal. Interspersed among its epithelial cells are goblet cells, which secrete mucus and fluid into the lumen, and enteroendocrine cells, which secrete hormones into the interstitial spaces between cells. Epithelial cells have a very brief lifespan, averaging from only a couple of days (in the mouth) to about a week (in the gut). This process of rapid renewal helps preserve the health of the alimentary canal, despite the wear and tear resulting from continued contact with foodstuffs.

Lamina propria—In addition to loose connective tissue, the lamina propria contains numerous blood and lymphatic vessels that transport nutrients absorbed through the alimentary canal to other parts of the body. The lamina propria also serves an immune function by housing clusters of lymphocytes, making up the mucosa-associated lymphoid tissue (MALT). These lymphocyte clusters are particularly substantial in the distal ileum where they are known as Peyer's patches. When you consider that the alimentary canal is exposed to foodborne bacteria and other foreign matter, it is not hard to appreciate why the immune system has evolved a means of defending against the pathogens encountered within it.

Muscularis mucosa—This thin layer of smooth muscle is in a constant state of tension, pulling the mucosa of the stomach and small intestine into undulating folds. These folds dramatically increase the surface area available for digestion and absorption.

As its name implies, the **submucosa** lies immediately beneath the mucosa. A broad layer of dense connective tissue, it connects the overlying mucosa to the underlying muscularis. It includes blood and lymphatic vessels (which transport absorbed nutrients), and a scattering of submucosal glands that release digestive secretions. Additionally, it serves as a conduit for a dense branching network of nerves, the submucosal plexus, which functions as described below.

The third layer of the alimentary canal is the **muscularis** (also called the muscularis externa). The muscularis in the small intestine is made up of a double layer of smooth muscle: an inner circular layer and an outer longitudinal layer. The contractions of these layers promote mechanical digestion, expose more of the food to digestive chemicals, and move the food along the canal. In the most proximal and distal regions of the alimentary canal, including the mouth, pharynx, anterior part of the esophagus, and external anal sphincter, the muscularis is made up of skeletal muscle, which gives you voluntary control over swallowing and defecation. The basic two-layer structure found in the small intestine is modified in the organs proximal and distal to it. The stomach is equipped for its churning function by the addition of a third layer, the oblique muscle. While the colon has two layers like the small intestine, its longitudinal layer

is segregated into three narrow parallel bands, the tenia coli, which make it look like a series of pouches rather than a simple tube.

The **serosa** is the portion of the alimentary canal superficial to the muscularis. Present only in the region of the alimentary canal within the abdominal cavity, it consists of a layer of visceral peritoneum overlying a layer of loose connective tissue. Instead of serosa, the mouth, pharynx, and esophagus have a dense sheath of collagen fibers called the adventitia. These tissues serve to hold the alimentary canal in place near the ventral surface of the vertebral column.

Nerve Supply

As soon as food enters the mouth, it is detected by receptors that send impulses along the sensory neurons of cranial nerves. Without these nerves, not only would your food be without taste, but you would also be unable to feel either the food or the structures of your mouth, and you would be unable to avoid biting yourself as you chew, an action enabled by the motor branches of cranial nerves.

Intrinsic innervation of much of the alimentary canal is provided by the enteric nervous system, which runs from the esophagus to the anus, and contains approximately 100 million motor, sensory, and interneurons (unique to this system compared to all other parts of the peripheral nervous system). These enteric neurons are grouped into two plexuses. The **myenteric plexus** (plexus of Auerbach) lies in the muscularis layer of the alimentary canal and is responsible for **motility**, especially the rhythm and force of the contractions of the muscularis. The **submucosal plexus** (plexus of Meissner) lies in the submucosal layer and is responsible for regulating digestive secretions and reacting to the presence of food (see [link]).

Extrinsic innervations of the alimentary canal are provided by the autonomic nervous system, which includes both sympathetic and parasympathetic nerves. In general, sympathetic activation (the fight-or-flight response) restricts the activity of enteric neurons, thereby decreasing GI secretion and motility. In contrast, parasympathetic activation (the rest-

and-digest response) increases GI secretion and motility by stimulating neurons of the enteric nervous system.

Blood Supply

The blood vessels serving the digestive system have two functions. They transport the protein and carbohydrate nutrients absorbed by mucosal cells after food is digested in the lumen. Lipids are absorbed via lacteals, tiny structures of the lymphatic system. The blood vessels’ second function is to supply the organs of the alimentary canal with the nutrients and oxygen needed to drive their cellular processes.

Specifically, the more anterior parts of the alimentary canal are supplied with blood by arteries branching off the aortic arch and thoracic aorta. Below this point, the alimentary canal is supplied with blood by arteries branching from the abdominal aorta. The celiac trunk services the liver, stomach, and duodenum, whereas the superior and inferior mesenteric arteries supply blood to the remaining small and large intestines.

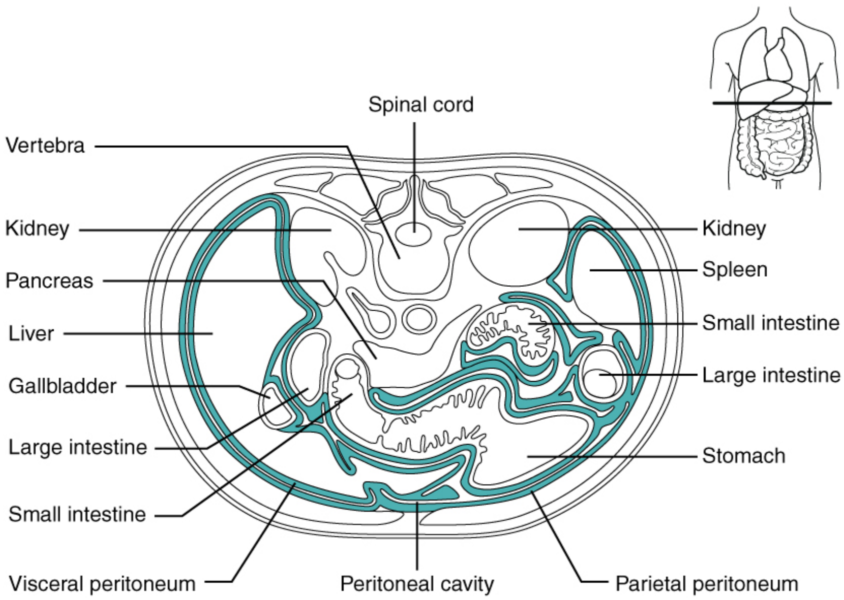
The veins that collect nutrient-rich blood from the small intestine (where most absorption occurs) empty into the hepatic portal system. This venous network takes the blood into the liver where the nutrients are either processed or stored for later use. Only then does the blood drained from the alimentary canal viscera circulate back to the heart. To appreciate just how demanding the digestive process is on the cardiovascular system, consider that while you are “resting and digesting,” about one-fourth of the blood pumped with each heartbeat enters arteries serving the intestines.

The Peritoneum

The digestive organs within the abdominal cavity are held in place by the peritoneum, a broad serous membranous sac made up of squamous epithelial tissue surrounded by connective tissue. It is composed of two different regions: the parietal peritoneum, which lines the abdominal wall, and the visceral peritoneum, which envelopes the abdominal organs ([link]). The peritoneal cavity is the space bounded by the visceral and parietal

peritoneal surfaces. A few milliliters of watery fluid act as a lubricant to minimize friction between the serosal surfaces of the peritoneum.

The Peritoneum



A cross-section of the abdomen shows the relationship between abdominal organs and the peritoneum (darker lines).

Note:

Disorders of the…

Digestive System: Peritonitis

Inflammation of the peritoneum is called peritonitis. Chemical peritonitis can develop any time the wall of the alimentary canal is breached, allowing the contents of the lumen entry into the peritoneal cavity. For example, when an ulcer perforates the stomach wall, gastric juices spill into the peritoneal cavity. Hemorrhagic peritonitis occurs after a ruptured tubal pregnancy or traumatic injury to the liver or spleen fills the peritoneal cavity with blood. Even more severe peritonitis is associated with bacterial infections seen with appendicitis, colonic diverticulitis, and pelvic inflammatory disease (infection of uterine tubes, usually by sexually

transmitted bacteria). Peritonitis is life threatening and often results in emergency surgery to correct the underlying problem and intensive antibiotic therapy. When your great grandparents and even your parents were young, the mortality from peritonitis was high. Aggressive surgery, improvements in anesthesia safety, the advance of critical care expertise, and antibiotics have greatly improved the mortality rate from this condition. Even so, the mortality rate still ranges from 30 to 40 percent.

The visceral peritoneum includes multiple large folds that envelope various abdominal organs, holding them to the dorsal surface of the body wall. Within these folds are blood vessels, lymphatic vessels, and nerves that innervate the organs with which they are in contact, supplying their adjacent organs. The five major peritoneal folds are described in [link]. Note that during fetal development, certain digestive structures, including the first portion of the small intestine (called the duodenum), the pancreas, and portions of the large intestine (the ascending and descending colon, and the rectum) remain completely or partially posterior to the peritoneum. Thus, the location of these organs is described as **retroperitoneal**.

The Five Major Peritoneal Folds

Fold	Description
Greater omentum	Apron-like structure that lies superficial to the small intestine and transverse colon; a site of fat deposition in people who are overweight
Falciform ligament	Anchors the liver to the anterior abdominal wall and inferior border of the diaphragm

The Five Major Peritoneal Folds	
Fold	**Description**
Lesser omentum	Suspends the stomach from the inferior border of the liver; provides a pathway for structures connecting to the liver
Mesentery	Vertical band of tissue anterior to the lumbar vertebrae and anchoring all of the small intestine except the initial portion (the duodenum)
Mesocolon	Attaches two portions of the large intestine (the transverse and sigmoid colon) to the posterior abdominal wall

Note:

By clicking on this link you can watch a short video of what happens to the food you eat, as it passes from your mouth to your intestine. Along the way, note how the food changes consistency and form. How does this change in consistency facilitate your gaining nutrients from food?

Chapter Review

The digestive system includes the organs of the alimentary canal and accessory structures. The alimentary canal forms a continuous tube that is

open to the outside environment at both ends. The organs of the alimentary canal are the mouth, pharynx, esophagus, stomach, small intestine, and large intestine. The accessory digestive structures include the teeth, tongue, salivary glands, liver, pancreas, and gallbladder. The wall of the alimentary canal is composed of four basic tissue layers: mucosa, submucosa, muscularis, and serosa. The enteric nervous system provides intrinsic innervation, and the autonomic nervous system provides extrinsic innervation.

Interactive Link Questions

Exercise:

Problem:

By clicking on this link, you can watch a short video of what happens to the food you eat as it passes from your mouth to your intestine. Along the way, note how the food changes consistency and form. How does this change in consistency facilitate your gaining nutrients from food?

Solution:

Answers may vary.

Review Questions

Exercise:

Problem:

Which of these organs is not considered an accessory digestive structure?

a. mouth
b. salivary glands
c. pancreas
d. liver

Solution:

A

Exercise:

Problem:

Which of the following organs is supported by a layer of adventitia rather than serosa?

a. esophagus
b. stomach
c. small intestine
d. large intestine

Solution:

A

Exercise:

Problem: Which of the following membranes covers the stomach?

a. falciform ligament
b. mesocolon
c. parietal peritoneum
d. visceral peritoneum

Solution:

D

Critical Thinking Questions

Exercise:

Problem:

Explain how the enteric nervous system supports the digestive system. What might occur that could result in the autonomic nervous system having a negative impact on digestion?

Solution:

The enteric nervous system helps regulate alimentary canal motility and the secretion of digestive juices, thus facilitating digestion. If a person becomes overly anxious, sympathetic innervation of the alimentary canal is stimulated, which can result in a slowing of digestive activity.

Exercise:

Problem:

What layer of the alimentary canal tissue is capable of helping to protect the body against disease, and through what mechanism?

Solution:

The lamina propria of the mucosa contains lymphoid tissue that makes up the MALT and responds to pathogens encountered in the alimentary canal.

Glossary

accessory digestive organ
: includes teeth, tongue, salivary glands, gallbladder, liver, and pancreas

alimentary canal
: continuous muscular digestive tube that extends from the mouth to the anus

motility

movement of food through the GI tract

mucosa
innermost lining of the alimentary canal

muscularis
muscle (skeletal or smooth) layer of the alimentary canal wall

myenteric plexus
(plexus of Auerbach) major nerve supply to alimentary canal wall; controls motility

retroperitoneal
located posterior to the peritoneum

serosa
outermost layer of the alimentary canal wall present in regions within the abdominal cavity

submucosa
layer of dense connective tissue in the alimentary canal wall that binds the overlying mucosa to the underlying muscularis

submucosal plexus
(plexus of Meissner) nerve supply that regulates activity of glands and smooth muscle

Digestive System Processes and Regulation
By the end of this section, you will be able to:

- Discuss six fundamental activities of the digestive system, giving an example of each
- Compare and contrast the neural and hormonal controls involved in digestion

The digestive system uses mechanical and chemical activities to break food down into absorbable substances during its journey through the digestive system. [link] provides an overview of the basic functions of the digestive organs.

Note:

Visit this site for an overview of digestion of food in different regions of the digestive tract. Note the route of non-fat nutrients from the small intestine to their release as nutrients to the body.

Functions of the Digestive Organs		
Organ	**Major functions**	**Other functions**

Functions of the Digestive Organs		
Organ	**Major functions**	**Other functions**
Mouth	Ingests food Chews and mixes food Begins chemical breakdown of carbohydrates Moves food into the pharynx Begins breakdown of lipids via lingual lipase	Moistens and dissolves food, allowing you to taste it Cleans and lubricates the teeth and oral cavity Has some antimicrobial activity
Pharynx	Propels food from the oral cavity to the esophagus	Lubricates food and passageways
Esophagus	Propels food to the stomach	Lubricates food and passageways

Functions of the Digestive Organs		
Organ	**Major functions**	**Other functions**
Stomach	Mixes and churns food with gastric juices to form chyme Begins chemical breakdown of proteins Releases food into the duodenum as chyme Absorbs some fat-soluble substances (for example, alcohol, aspirin) Possesses antimicrobial functions	Stimulates protein-digesting enzymes Secretes intrinsic factor required for vitamin B_{12} absorption in small intestine

Functions of the Digestive Organs		
Organ	**Major functions**	**Other functions**
Small intestine	Mixes chyme with digestive juices Propels food at a rate slow enough for digestion and absorption Absorbs breakdown products of carbohydrates, proteins, lipids, and nucleic acids, along with vitamins, minerals, and water Performs physical digestion via segmentation	Provides optimal medium for enzymatic activity

Functions of the Digestive Organs		
Organ	**Major functions**	**Other functions**
Accessory organs	Liver: produces bile salts, which emulsify lipids, aiding their digestion and absorption Gallbladder: stores, concentrates, and releases bile Pancreas: produces digestive enzymes and bicarbonate	Bicarbonate-rich pancreatic juices help neutralize acidic chyme and provide optimal environment for enzymatic activity
Large intestine	Further breaks down food residues Absorbs most residual water, electrolytes, and vitamins produced by enteric bacteria Propels feces toward rectum Eliminates feces	Food residue is concentrated and temporarily stored prior to defecation Mucus eases passage of feces through colon

Digestive Processes

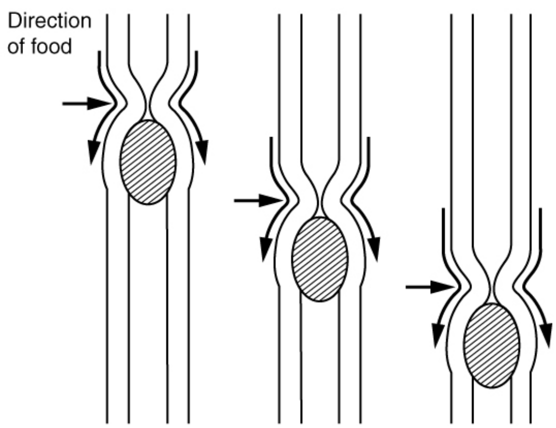
The processes of digestion include six activities: ingestion, propulsion, mechanical or physical digestion, chemical digestion, absorption, and

defecation.

The first of these processes, **ingestion**, refers to the entry of food into the alimentary canal through the mouth. There, the food is chewed and mixed with saliva, which contains enzymes that begin breaking down the carbohydrates in the food plus some lipid digestion via lingual lipase. Chewing increases the surface area of the food and allows an appropriately sized bolus to be produced.

Food leaves the mouth when the tongue and pharyngeal muscles propel it into the esophagus. This act of swallowing, the last voluntary act until defecation, is an example of **propulsion**, which refers to the movement of food through the digestive tract. It includes both the voluntary process of swallowing and the involuntary process of peristalsis. **Peristalsis** consists of sequential, alternating waves of contraction and relaxation of alimentary wall smooth muscles, which act to propel food along ([link]). These waves also play a role in mixing food with digestive juices. Peristalsis is so powerful that foods and liquids you swallow enter your stomach even if you are standing on your head.

Peristalsis



Peristalsis moves food through the digestive tract with alternating waves of muscle contraction and relaxation.

Digestion includes both mechanical and chemical processes. **Mechanical digestion** is a purely physical process that does not change the chemical nature of the food. Instead, it makes the food smaller to increase both surface area and mobility. It includes **mastication**, or chewing, as well as tongue movements that help break food into smaller bits and mix food with saliva. Although there may be a tendency to think that mechanical digestion is limited to the first steps of the digestive process, it occurs after the food leaves the mouth, as well. The mechanical churning of food in the stomach serves to further break it apart and expose more of its surface area to digestive juices, creating an acidic “soup” called **chyme**. **Segmentation**, which occurs mainly in the small intestine, consists of localized contractions of circular muscle of the muscularis layer of the alimentary canal. These contractions isolate small sections of the intestine, moving their contents back and forth while continuously subdividing, breaking up, and mixing the contents. By moving food back and forth in the intestinal lumen, segmentation mixes food with digestive juices and facilitates absorption.

In **chemical digestion**, starting in the mouth, digestive secretions break down complex food molecules into their chemical building blocks (for example, proteins into separate amino acids). These secretions vary in composition, but typically contain water, various enzymes, acids, and salts. The process is completed in the small intestine.

Food that has been broken down is of no value to the body unless it enters the bloodstream and its nutrients are put to work. This occurs through the process of **absorption**, which takes place primarily within the small intestine. There, most nutrients are absorbed from the lumen of the alimentary canal into the bloodstream through the epithelial cells that make up the mucosa. Lipids are absorbed into lacteals and are transported via the lymphatic vessels to the bloodstream (the subclavian veins near the heart). The details of these processes will be discussed later.

In **defecation**, the final step in digestion, undigested materials are removed from the body as feces.

Note:

Aging and the…

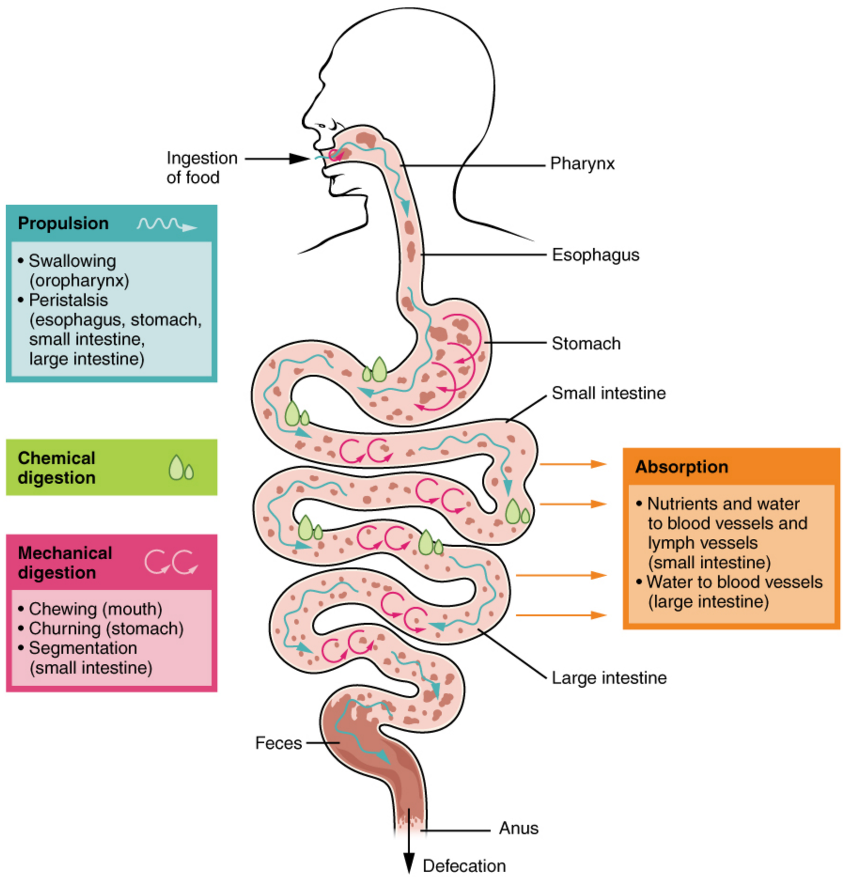
Digestive System: From Appetite Suppression to Constipation

Age-related changes in the digestive system begin in the mouth and can affect virtually every aspect of the digestive system. Taste buds become less sensitive, so food isn't as appetizing as it once was. A slice of pizza is a challenge, not a treat, when you have lost teeth, your gums are diseased, and your salivary glands aren't producing enough saliva. Swallowing can be difficult, and ingested food moves slowly through the alimentary canal because of reduced strength and tone of muscular tissue. Neurosensory feedback is also dampened, slowing the transmission of messages that stimulate the release of enzymes and hormones.

Pathologies that affect the digestive organs—such as hiatal hernia, gastritis, and peptic ulcer disease—can occur at greater frequencies as you age. Problems in the small intestine may include duodenal ulcers, maldigestion, and malabsorption. Problems in the large intestine include hemorrhoids, diverticular disease, and constipation. Conditions that affect the function of accessory organs—and their abilities to deliver pancreatic enzymes and bile to the small intestine—include jaundice, acute pancreatitis, cirrhosis, and gallstones.

In some cases, a single organ is in charge of a digestive process. For example, ingestion occurs only in the mouth and defecation only in the anus. However, most digestive processes involve the interaction of several organs and occur gradually as food moves through the alimentary canal ([link]).

Digestive Processes



The digestive processes are ingestion, propulsion, mechanical digestion, chemical digestion, absorption, and defecation.

Some chemical digestion occurs in the mouth. Some absorption can occur in the mouth and stomach, for example, alcohol and aspirin.

Regulatory Mechanisms

Neural and endocrine regulatory mechanisms work to maintain the optimal conditions in the lumen needed for digestion and absorption. These regulatory mechanisms, which stimulate digestive activity through mechanical and chemical activity, are controlled both extrinsically and intrinsically.

Neural Controls

The walls of the alimentary canal contain a variety of sensors that help regulate digestive functions. These include mechanoreceptors, chemoreceptors, and osmoreceptors, which are capable of detecting mechanical, chemical, and osmotic stimuli, respectively. For example, these receptors can sense when the presence of food has caused the stomach to expand, whether food particles have been sufficiently broken down, how much liquid is present, and the type of nutrients in the food (lipids, carbohydrates, and/or proteins). Stimulation of these receptors provokes an appropriate reflex that furthers the process of digestion. This may entail sending a message that activates the glands that secrete digestive juices into the lumen, or it may mean the stimulation of muscles within the alimentary canal, thereby activating peristalsis and segmentation that move food along the intestinal tract.

The walls of the entire alimentary canal are embedded with nerve plexuses that interact with the central nervous system and other nerve plexuses—either within the same digestive organ or in different ones. These interactions prompt several types of reflexes. Extrinsic nerve plexuses orchestrate long reflexes, which involve the central and autonomic nervous systems and work in response to stimuli from outside the digestive system. Short reflexes, on the other hand, are orchestrated by intrinsic nerve plexuses within the alimentary canal wall. These two plexuses and their connections were introduced earlier as the enteric nervous system. Short reflexes regulate activities in one area of the digestive tract and may coordinate local peristaltic movements and stimulate digestive secretions. For example, the sight, smell, and taste of food initiate long reflexes that begin with a sensory neuron delivering a signal to the medulla oblongata. The response to the signal is to stimulate cells in the stomach to begin secreting digestive juices in preparation for incoming food. In contrast, food that distends the stomach initiates short reflexes that cause cells in the stomach wall to increase their secretion of digestive juices.

Hormonal Controls

A variety of hormones are involved in the digestive process. The main digestive hormone of the stomach is gastrin, which is secreted in response to the presence of food. Gastrin stimulates the secretion of gastric acid by the parietal cells of the stomach mucosa. Other GI hormones are produced and act upon the gut and its accessory organs. Hormones produced by the duodenum include secretin, which stimulates a watery secretion of bicarbonate by the pancreas; cholecystokinin (CCK), which stimulates the secretion of pancreatic enzymes and bile from the liver and release of bile from the gallbladder; and gastric inhibitory peptide, which inhibits gastric secretion and slows gastric emptying and motility. These GI hormones are secreted by specialized epithelial cells, called endocrinocytes, located in the mucosal epithelium of the stomach and small intestine. These hormones then enter the bloodstream, through which they can reach their target organs.

Chapter Review

The digestive system ingests and digests food, absorbs released nutrients, and excretes food components that are indigestible. The six activities involved in this process are ingestion, motility, mechanical digestion, chemical digestion, absorption, and defecation. These processes are regulated by neural and hormonal mechanisms.

Interactive Link Questions

Exercise:

Problem:

Visit this site for an overview of digestion of food in different regions of the digestive tract. Note the route of non-fat nutrients from the small intestine to their release as nutrients to the body.

Solution:

Answers may vary.

Multiple Choice

Exercise:

Problem: Which of these processes occurs in the mouth?

a. ingestion
b. mechanical digestion
c. chemical digestion
d. all of the above

Solution:

D

Exercise:

Problem:

Which of these processes occurs throughout most of the alimentary canal?

a. ingestion
b. propulsion
c. segmentation
d. absorption

Solution:

B

Exercise:

Problem:

Which of the following stimuli activates sensors in the walls of digestive organs?

a. breakdown products of digestion
b. distension
c. pH of chyme
d. all of the above

Solution:

D

Exercise:

Problem:

Which of these statements about reflexes in the GI tract is false?

a. Short reflexes are provoked by nerves near the GI tract.
b. Short reflexes are mediated by the enteric nervous system.
c. Food that distends the stomach initiates long reflexes.
d. Long reflexes can be provoked by stimuli originating outside the GI tract.

Solution:

C

Critical Thinking Questions

Exercise:

Problem:

Offer a theory to explain why segmentation occurs and peristalsis slows in the small intestine.

Solution:

The majority of digestion and absorption occurs in the small intestine. By slowing the transit of chyme, segmentation and a reduced rate of peristalsis allow time for these processes to occur.

Exercise:

Problem:

It has been several hours since you last ate. Walking past a bakery, you catch a whiff of freshly baked bread. What type of reflex is triggered, and what is the result?

Solution:

The smell of food initiates long reflexes, which result in the secretion of digestive juices.

Glossary

absorption
: passage of digested products from the intestinal lumen through mucosal cells and into the bloodstream or lacteals

chemical digestion
: enzymatic breakdown of food

chyme
: soupy liquid created when food is mixed with digestive juices

defecation
: elimination of undigested substances from the body in the form of feces

ingestion
: taking food into the GI tract through the mouth

mastication
: chewing

mechanical digestion
: chewing, mixing, and segmentation that prepares food for chemical digestion

peristalsis
: muscular contractions and relaxations that propel food through the GI tract

propulsion
: voluntary process of swallowing and the involuntary process of peristalsis that moves food through the digestive tract

segmentation
: alternating contractions and relaxations of non-adjacent segments of the intestine that move food forward and backward, breaking it apart and mixing it with digestive juices

The Mouth, Pharynx, and Esophagus
By the end of this section, you will be able to:

- Describe the structures of the mouth, including its three accessory digestive organs
- Group the 32 adult teeth according to name, location, and function
- Describe the process of swallowing, including the roles of the tongue, upper esophageal sphincter, and epiglottis
- Trace the pathway food follows from ingestion into the mouth through release into the stomach

In this section, you will examine the anatomy and functions of the three main organs of the upper alimentary canal—the mouth, pharynx, and esophagus—as well as three associated accessory organs—the tongue, salivary glands, and teeth.

The Mouth

The cheeks, tongue, and palate frame the mouth, which is also called the **oral cavity** (or buccal cavity). The structures of the mouth are illustrated in [link].

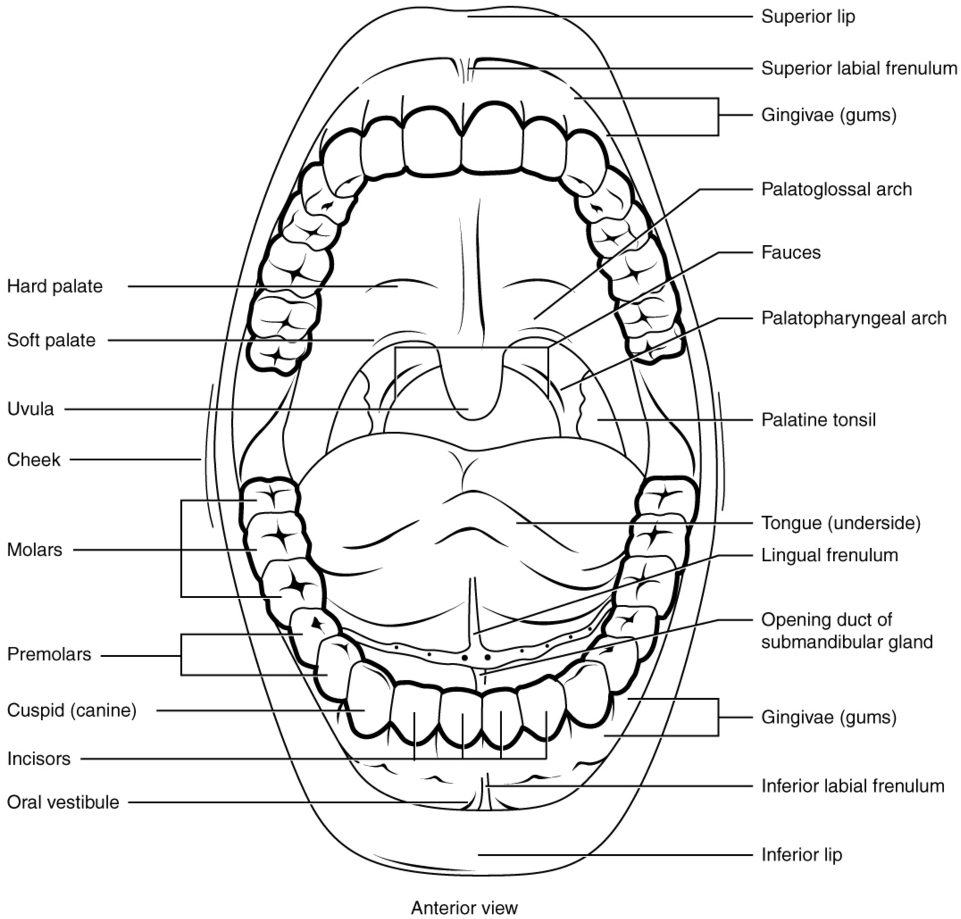
At the entrance to the mouth are the lips, or **labia** (singular = labium). Their outer covering is skin, which transitions to a mucous membrane in the mouth proper. Lips are very vascular with a thin layer of keratin; hence, the reason they are "red." They have a huge representation on the cerebral cortex, which probably explains the human fascination with kissing! The lips cover the orbicularis oris muscle, which regulates what comes in and goes out of the mouth. The **labial frenulum** is a midline fold of mucous membrane that attaches the inner surface of each lip to the gum. The cheeks make up the oral cavity’s sidewalls. While their outer covering is skin, their inner covering is mucous membrane. This membrane is made up of non-keratinized, stratified squamous epithelium. Between the skin and mucous membranes are connective tissue and buccinator muscles. The next time you eat some food, notice how the buccinator muscles in your cheeks and the orbicularis oris muscle in your lips contract, helping you keep the food

from falling out of your mouth. Additionally, notice how these muscles work when you are speaking.

The pocket-like part of the mouth that is framed on the inside by the gums and teeth, and on the outside by the cheeks and lips is called the **oral vestibule**. Moving farther into the mouth, the opening between the oral cavity and throat (oropharynx) is called the **fauces** (like the kitchen "faucet"). The main open area of the mouth, or oral cavity proper, runs from the gums and teeth to the fauces.

When you are chewing, you do not find it difficult to breathe simultaneously. The next time you have food in your mouth, notice how the arched shape of the roof of your mouth allows you to handle both digestion and respiration at the same time. This arch is called the palate. The anterior region of the palate serves as a wall (or septum) between the oral and nasal cavities as well as a rigid shelf against which the tongue can push food. It is created by the maxillary and palatine bones of the skull and, given its bony structure, is known as the hard palate. If you run your tongue along the roof of your mouth, you'll notice that the hard palate ends in the posterior oral cavity, and the tissue becomes fleshier. This part of the palate, known as the **soft palate**, is composed mainly of skeletal muscle. You can therefore manipulate, subconsciously, the soft palate—for instance, to yawn, swallow, or sing (see [link]).

Mouth



The mouth includes the lips, tongue, palate, gums, and teeth.

A fleshy bead of tissue called the uvula drops down from the center of the posterior edge of the soft palate. Although some have suggested that the uvula is a vestigial organ, it serves an important purpose. When you swallow, the soft palate and uvula move upward, helping to keep foods and liquid from entering the nasal cavity. Unfortunately, it can also contribute to the sound produced by snoring. Two muscular folds extend downward from the soft palate, on either side of the uvula. Toward the front, the **palatoglossal arch** lies next to the base of the tongue; behind it, the **palatopharyngeal arch** forms the superior and lateral margins of the fauces. Between these two arches are the palatine tonsils, clusters of

lymphoid tissue that protect the pharynx. The lingual tonsils are located at the base of the tongue.

The Tongue

Perhaps you have heard it said that the **tongue** is the strongest muscle in the body. Those who stake this claim cite its strength proportionate to its size. Although it is difficult to quantify the relative strength of different muscles, it remains indisputable that the tongue is a workhorse, facilitating ingestion, mechanical digestion, chemical digestion (lingual lipase), sensation (of taste, texture, and temperature of food), swallowing, and vocalization.

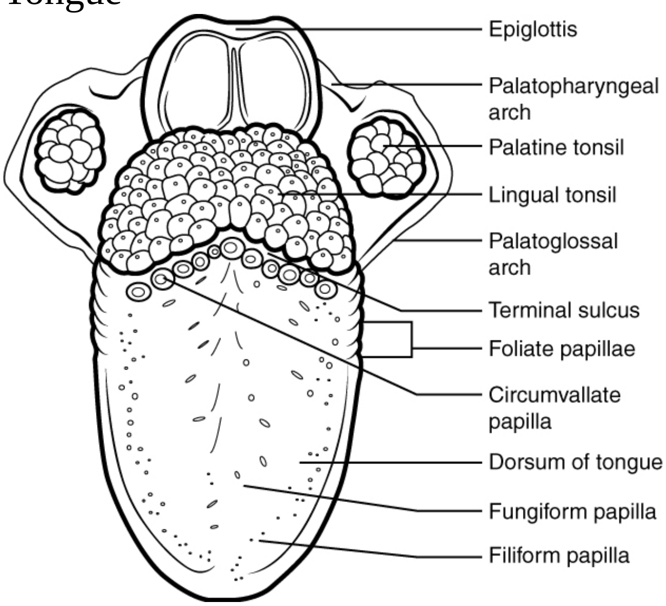
The tongue is attached to the mandible, the styloid processes of the temporal bones, and the hyoid bone. The hyoid is unique in that it only distantly/indirectly articulates with other bones. The tongue is positioned over the floor of the oral cavity. A medial septum extends the entire length of the tongue, dividing it into symmetrical halves.

Beneath its mucous membrane covering, each half of the tongue is composed of the same number and type of intrinsic and extrinsic skeletal muscles. The intrinsic muscles (those within the tongue) are the longitudinalis inferior, longitudinalis superior, transversus linguae, and verticalis linguae muscles. These allow you to change the size and shape of your tongue, as well as to stick it out, if you wish. Having such a flexible tongue facilitates both swallowing and speech.

As you learned in your study of the muscular system, the extrinsic muscles of the tongue are the mylohyoid, hyoglossus, styloglossus, and genioglossus muscles. These muscles originate outside the tongue and insert into connective tissues within the tongue. The mylohyoid is responsible for raising the tongue, the hyoglossus pulls it down and back, the styloglossus pulls it up and back, and the genioglossus pulls it forward. Working in concert, these muscles perform three important digestive functions in the mouth: (1) position food for optimal chewing, (2) gather food into a **bolus** (rounded mass), and (3) position food so it can be swallowed.

The top and sides of the tongue are studded with papillae, extensions of lamina propria of the mucosa, which are covered in stratified squamous epithelium ([link]). Fungiform papillae, which are mushroom shaped, cover a large area of the tongue; they tend to be larger toward the rear of the tongue and smaller on the tip and sides. In contrast, filiform papillae are long and thin. Fungiform papillae contain taste buds, and filiform papillae have touch receptors that help the tongue move food around in the mouth. The filiform papillae create an abrasive surface that performs mechanically, much like a cat's rough tongue that is used for grooming. Lingual glands in the lamina propria of the tongue secrete mucus and a watery serous fluid that contains the enzyme **lingual lipase**, which plays a minor role in breaking down triglycerides but does not begin working until it is activated in the stomach. A fold of mucous membrane on the underside of the tongue, the **lingual frenulum**, tethers the tongue to the floor of the mouth. People with the congenital anomaly ankyloglossia, also known by the non-medical term "tongue tie," have a lingual frenulum that is too short or otherwise malformed. Severe ankyloglossia can impair speech and must be corrected with surgery.

Tongue



This superior view of the tongue shows the locations and types of lingual papillae.

The Salivary Glands

Many small **salivary glands** are housed within the mucous membranes of the mouth and tongue. These minor exocrine glands are constantly secreting saliva, either directly into the oral cavity or indirectly through ducts, even while you sleep. In fact, an average of 1 to 1.5 liters of saliva is secreted each day. Usually just enough saliva is present to moisten the mouth and teeth. Secretion increases when you eat, because saliva is essential to moisten food and initiate the chemical breakdown of carbohydrates. Small amounts of saliva are also secreted by the labial glands in the lips. In addition, the buccal glands in the cheeks, palatal glands in the palate, and lingual glands in the tongue help ensure that all areas of the mouth are supplied with adequate saliva.

The Major Salivary Glands

Outside the oral mucosa are three pairs of major salivary glands, which secrete the majority of saliva into ducts that open into the mouth:

- The **submandibular glands**, which are in the floor of the mouth, secrete saliva into the mouth through the submandibular ducts.
- The **sublingual glands**, which lie below the tongue, use the lesser sublingual ducts to secrete saliva into the oral cavity.
- The **parotid glands** lie between the skin and the masseter muscle, near the ears. They secrete saliva into the mouth through the parotid duct, which is located near the second upper molar tooth ([link]).

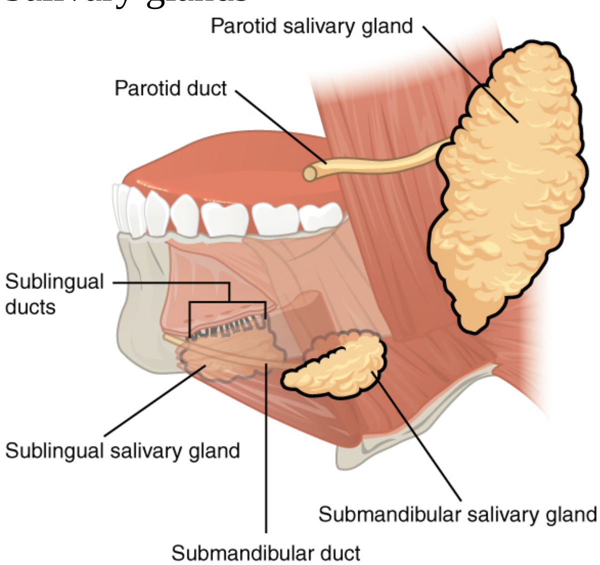
Saliva

Saliva is essentially (98 to 99.5 percent) water. The remaining 4.5 percent is a complex mixture of ions, glycoproteins, enzymes, growth factors, and waste products. Perhaps the most important ingredient in saliva from the

perspective of digestion is the enzyme **salivary amylase**, which initiates the breakdown of carbohydrates. Food does not spend enough time in the mouth to allow all the carbohydrates to break down, but salivary amylase continues acting until it is inactivated by stomach acids. Bicarbonate and phosphate ions function as chemical buffers, maintaining saliva at a pH between 6.35 and 6.85. Salivary mucus helps lubricate food, facilitating movement in the mouth, bolus formation, and swallowing. Saliva contains immunoglobulin A, which prevents microbes from penetrating the epithelium, and lysozyme, which makes saliva antimicrobial. Saliva also contains epidermal growth factor, which might have given rise to the adage “a mother’s kiss can heal a wound.”

Each of the major salivary glands secretes a unique formulation of saliva according to its cellular makeup. For example, the parotid glands secrete a watery solution that contains salivary amylase. The submandibular glands have cells similar to those of the parotid glands, as well as mucus-secreting cells. Therefore, saliva secreted by the submandibular glands also contains amylase but in a liquid thickened with mucus. The sublingual glands contain mostly mucous cells, and they secrete the thickest saliva with the least amount of salivary amylase.

Salivary glands



The major salivary glands are located outside the oral mucosa

and deliver saliva into the
mouth through ducts.

Note:
Homeostatic Imbalances
The Parotid Glands: Mumps
Infections of the nasal passages and pharynx can attack any salivary gland. The parotid glands are the usual site of infection with the virus that causes mumps (paramyxovirus). Mumps manifests by enlargement and inflammation of the parotid glands, causing a characteristic swelling between the ears and the jaw. Symptoms include fever and throat pain, which can be severe when swallowing acidic substances such as orange juice.
In about one-third of men who are past puberty, mumps also causes testicular inflammation, typically affecting only one testis and rarely resulting in sterility. With the increasing use and effectiveness of mumps vaccines, the incidence of mumps has decreased dramatically. According to the U.S. Centers for Disease Control and Prevention (CDC), the number of mumps cases dropped from more than 150,000 in 1968 to fewer than 1700 in 1993 to only 11 reported cases in 2011.

Regulation of Salivation

The autonomic nervous system regulates **salivation** (the secretion of saliva). In the absence of food, parasympathetic stimulation keeps saliva flowing at just the right level for comfort as you speak, swallow, sleep, and generally go about life. Over-salivation can occur, for example, if you are stimulated by the smell of food, but that food is not available for you to eat. Drooling is an extreme instance of the overproduction of saliva. During times of stress, such as before speaking in public, sympathetic stimulation takes over, reducing salivation and producing the symptom of dry mouth often associated with anxiety. When you are dehydrated, salivation is

reduced, causing the mouth to feel dry and prompting you to take action to quench your thirst.

Salivation can be stimulated by the sight, smell, and taste of food. It can even be stimulated by thinking about food. You might notice whether reading about food and salivation right now has had any effect on your production of saliva.

How does the salivation process work while you are eating? Food contains chemicals that stimulate taste receptors on the tongue, which send impulses to the superior and inferior salivatory nuclei in the brain stem. These two nuclei then send back parasympathetic impulses through fibers in the glossopharyngeal and facial nerves, which stimulate salivation. Even after you swallow food, salivation is increased to cleanse the mouth and to water down and neutralize any irritating chemical remnants, such as that hot sauce in your burrito. Most saliva is swallowed along with food and is reabsorbed, so that fluid is not lost.

The Teeth

The teeth, or **dentes** (singular = dens), are organs similar to bones that you use to tear, grind, and otherwise mechanically break down food.

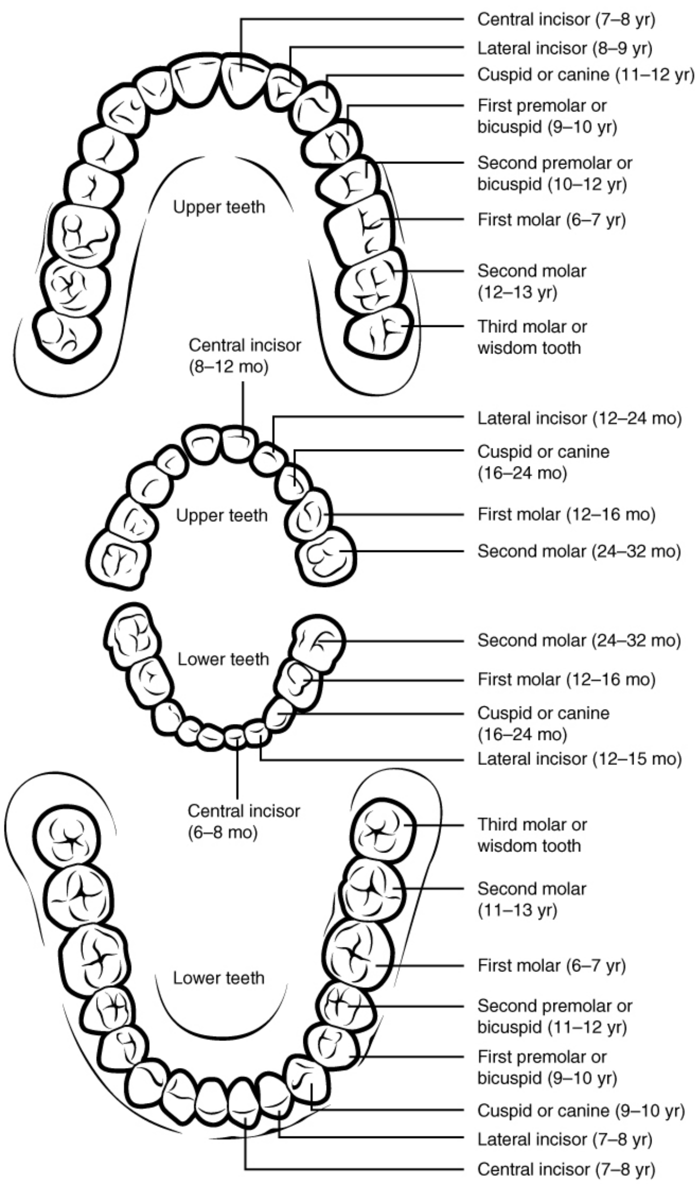
Types of Teeth

During the course of your lifetime, you have two sets of teeth (one set of teeth is a **dentition**). Your 20 **deciduous teeth**, or baby teeth, first begin to appear at about 6 months of age. Between approximately age 6 and 12, these teeth are replaced by 32 **permanent teeth**. Moving from the center of the mouth toward the side, these are as follows ([link]):

- The eight **incisors**, four top and four bottom, are the sharp front teeth you use for biting into food.
- The four **cuspids** (or canines) flank the incisors and have a pointed edge (cusp) to tear up food. These fang-like teeth are superb for piercing tough or fleshy foods.

- Posterior to the cuspids are the eight **premolars** (or bicuspids), which have an overall flatter shape with two rounded cusps useful for mashing foods.
- The most posterior and largest are the 12 **molars**, which have several pointed cusps used to crush food so it is ready for swallowing. The third members of each set of three molars, top and bottom, are commonly referred to as the wisdom teeth, because their eruption is commonly delayed until early adulthood. It is not uncommon for wisdom teeth to fail to erupt; that is, they remain impacted. In these cases, the teeth are typically removed by orthodontic surgery.

Permanent and Deciduous Teeth



This figure of two human dentitions shows the arrangement of teeth in the maxilla and mandible, and the relationship between the deciduous and permanent teeth.

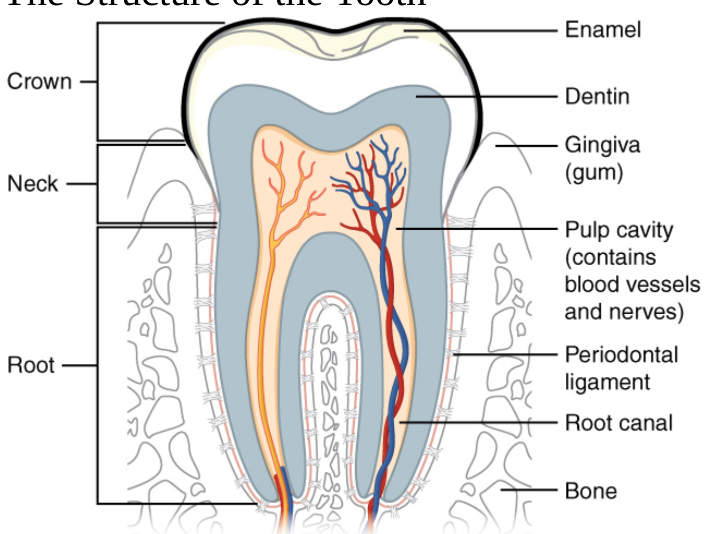
Anatomy of a Tooth

The teeth are secured in the alveolar processes (sockets) of the maxilla and the mandible. **Gingivae** (commonly called the gums) are soft tissues that line the alveolar processes and surround the necks of the teeth. Teeth are also held in their sockets by a connective tissue called the periodontal ligament.

The two main parts of a tooth are the **crown**, which is the portion projecting above the gum line, and the **root**, which is embedded within the maxilla and mandible. Both parts contain an inner **pulp cavity**, containing loose connective tissue through which run nerves and blood vessels. The region of the pulp cavity that runs through the root of the tooth is called the root canal. Surrounding the pulp cavity is **dentin**, a bone-like tissue. In the root of each tooth, the dentin is covered by an even harder bone-like layer called **cementum**. In the crown of each tooth, the dentin is covered by an outer layer of **enamel**, the hardest substance in the body ([link]).

Although enamel protects the underlying dentin and pulp cavity, it is still nonetheless susceptible to mechanical and chemical erosion, or what is known as tooth decay. The most common form, dental caries (cavities) develops when colonies of bacteria feeding on sugars in the mouth release acids that cause soft tissue inflammation and degradation of the calcium crystals of the enamel. The digestive functions of the mouth are summarized in [link].

The Structure of the Tooth



This longitudinal section through a

molar in its alveolar socket shows the relationships between enamel, dentin, and pulp.

Digestive Functions of the Mouth		
Structure	**Action**	**Outcome**
Lips and cheeks	Confine food between teeth	Food is chewed evenly during mastication
Salivary glands	Secrete saliva	Moisten and lubricate the lining of the mouth and pharynx Moisten, soften, and dissolve food Clean the mouth and teeth Salivary amylase breaks down starch
Tongue’s extrinsic muscles	Move tongue sideways, and in and out	Manipulate food for chewing Shape food into a bolus Manipulate food for swallowing

Digestive Functions of the Mouth		
Structure	**Action**	**Outcome**
Tongue's intrinsic muscles	Change tongue shape	Manipulate food for swallowing
Taste buds	Sense food in mouth and sense taste	Nerve impulses from taste buds are conducted to salivary nuclei in the brain stem and then to salivary glands, stimulating saliva secretion
Lingual glands	Secrete lingual lipase	Activated in the stomach Break down triglycerides into fatty acids and diglycerides
Teeth	Shred and crush food	Break down solid food into smaller particles for deglutition

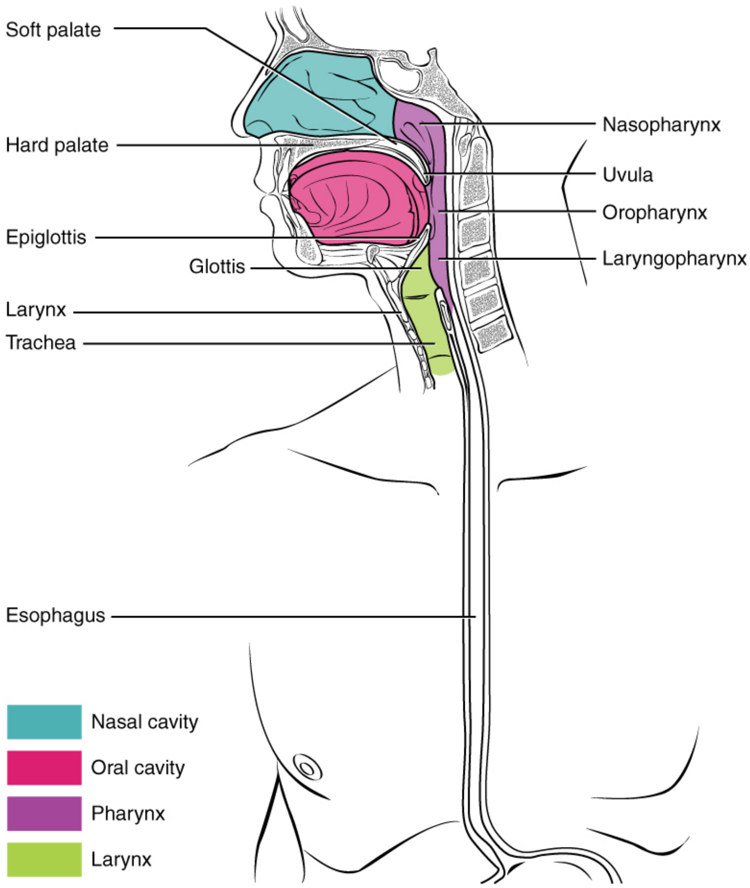
The Pharynx

The **pharynx** (throat) is involved in both digestion and respiration. It receives food and air from the mouth, and air from the nasal cavities. When food enters the pharynx, involuntary muscle contractions close off the air passageways.

A short tube of skeletal muscle lined with a mucous membrane, the pharynx runs from the posterior oral and nasal cavities to the opening of the esophagus and larynx. It has three subdivisions. The most superior, the

nasopharynx, is involved only in breathing and speech. The other two subdivisions, the **oropharynx** and the **laryngopharynx**, are used for both breathing and digestion. The oropharynx begins inferior to the nasopharynx and is continuous below with the laryngopharynx ([link]). The inferior border of the laryngopharynx connects to the esophagus, whereas the anterior portion connects to the larynx, allowing air to flow into the bronchial tree.

Pharynx



The pharynx runs from the nostrils to the esophagus and the larynx.

Histologically, the wall of the oropharynx is similar to that of the oral cavity. The mucosa includes a stratified squamous epithelium that is endowed with mucus-producing glands. During swallowing, the elevator skeletal muscles of the pharynx contract, raising and expanding the pharynx

to receive the bolus of food. Once received, these muscles relax and the constrictor muscles of the pharynx contract, forcing the bolus into the esophagus and initiating peristalsis.

Usually during swallowing, the soft palate and uvula rise reflexively to close off the entrance to the nasopharynx. At the same time, the larynx is pulled superiorly and the cartilaginous epiglottis, its most superior structure, folds inferiorly, covering the glottis (the opening to the larynx); this process effectively blocks access to the trachea and bronchi. When the food “goes down the wrong way,” it goes into the trachea. When food enters the trachea, the reaction is to cough, which usually forces the food up and out of the trachea, and back into the pharynx.

The Esophagus

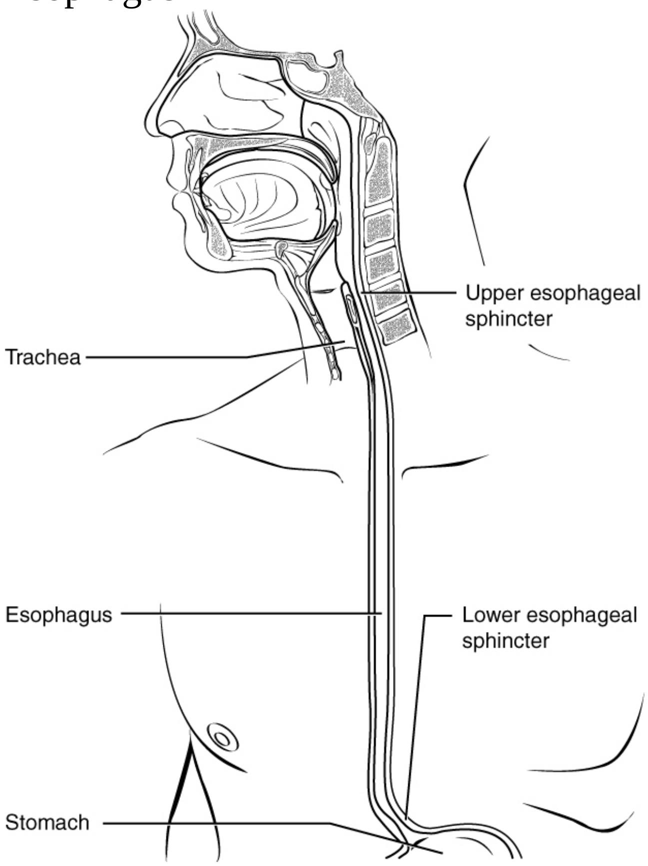
The **esophagus** is a muscular tube that connects the pharynx to the stomach. It is approximately 25.4 cm (10 in) in length, located posterior to the trachea, and remains in a collapsed form when not engaged in swallowing. As you can see in [link], the esophagus runs a mainly straight route through the mediastinum of the thorax. To enter the abdomen, the esophagus penetrates the diaphragm through an opening called the esophageal hiatus.

Passage of Food through the Esophagus

The **upper esophageal sphincter**, which is continuous with the inferior pharyngeal constrictor, controls the movement of food from the pharynx into the esophagus. The upper two-thirds of the esophagus consists of both smooth and skeletal muscle fibers, with the latter fading out in the bottom third of the esophagus. Rhythmic waves of peristalsis, which begin in the upper esophagus, propel the bolus of food toward the stomach. Meanwhile, secretions from the esophageal mucosa lubricate the esophagus and food. Food passes from the esophagus into the stomach at the **lower esophageal sphincter** (also called the gastroesophageal or cardiac sphincter). Recall that sphincters are muscles that surround tubes and serve as valves, closing the tube when the sphincters contract and opening it when they relax. The

lower esophageal sphincter relaxes to let food pass into the stomach, and then contracts to prevent stomach acids from backing up into the esophagus. Surrounding this sphincter is the muscular diaphragm, which helps close off the sphincter when no food is being swallowed. When the lower esophageal sphincter does not completely close, the stomach's contents can reflux (that is, back up into the esophagus), causing heartburn or gastroesophageal reflux disease (GERD).

Esophagus



The upper esophageal sphincter controls the movement of food from the pharynx to the esophagus. The lower esophageal sphincter controls the movement of food from the esophagus to the stomach.

Histology of the Esophagus

The mucosa of the esophagus is made up of an epithelial lining that contains non-keratinized, stratified squamous epithelium, with a layer of basal and parabasal cells. This epithelium protects against erosion from food particles. The mucosa's lamina propria contains mucus-secreting glands. The muscularis layer changes according to location: In the upper third of the esophagus, the muscularis is skeletal muscle. In the middle third, it is both skeletal and smooth muscle. In the lower third, it is smooth muscle. As mentioned previously, the most superficial layer of the esophagus is called the adventitia, not the serosa. In contrast to the stomach and intestines, the loose connective tissue of the adventitia is not covered by a fold of visceral peritoneum. The digestive functions of the esophagus are identified in [link].

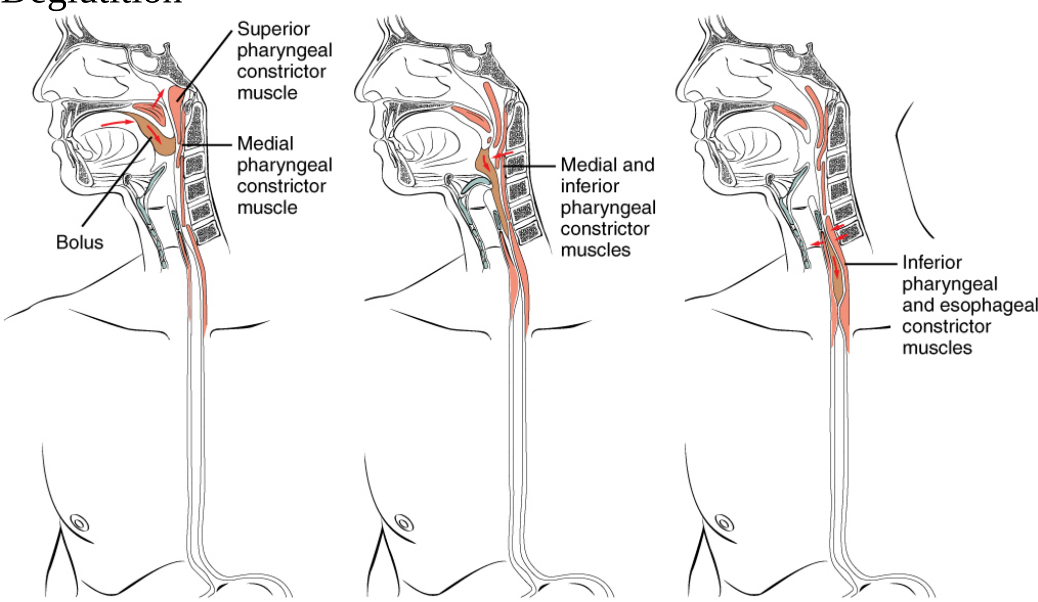
Digestive Functions of the Esophagus	
Action	**Outcome**
Upper esophageal sphincter relaxation	Allows the bolus to move from the laryngopharynx to the esophagus
Peristalsis	Propels the bolus through the esophagus
Lower esophageal sphincter relaxation	Allows the bolus to move from the esophagus into the stomach and prevents chime from entering the esophagus

Digestive Functions of the Esophagus	
Action	**Outcome**
Mucus secretion	Lubricates the esophagus, allowing easy passage of the bolus

Deglutition

Deglutition is another word for swallowing—the movement of food from the mouth to the stomach. The entire process takes about 4 to 8 seconds for solid or semisolid food, and about 1 second for very soft food and liquids. Although this sounds quick and effortless, deglutition is, in fact, a complex process that involves both the skeletal muscle of the tongue and the muscles of the pharynx and esophagus. It is aided by the presence of mucus and saliva. There are three stages in deglutition: the voluntary phase, the pharyngeal phase, and the esophageal phase ([link]). The autonomic nervous system controls the latter two phases.

Deglutition



Deglutition includes the voluntary phase and two involuntary phases: the pharyngeal phase and the esophageal phase.

The Voluntary Phase

The **voluntary phase** of deglutition (also known as the oral or buccal phase) is so called because you can control when you swallow food. In this phase, chewing has been completed and swallowing is set in motion. The tongue moves upward and backward against the palate, pushing the bolus to the back of the oral cavity and into the oropharynx. Other muscles keep the mouth closed and prevent food from falling out. At this point, the two involuntary phases of swallowing begin.

The Pharyngeal Phase

In the pharyngeal phase, stimulation of receptors in the oropharynx sends impulses to the deglutition center (a collection of neurons that controls swallowing) in the medulla oblongata. Impulses are then sent back to the uvula and soft palate, causing them to move upward and close off the nasopharynx. The laryngeal muscles also constrict to prevent aspiration of food into the trachea. At this point, deglutition apnea takes place, which means that breathing ceases for a very brief time. Contractions of the pharyngeal constrictor muscles move the bolus through the oropharynx and laryngopharynx. Relaxation of the upper esophageal sphincter then allows food to enter the esophagus.

The Esophageal Phase

The entry of food into the esophagus marks the beginning of the esophageal phase of deglutition and the initiation of peristalsis. As in the previous phase, the complex neuromuscular actions are controlled by the medulla oblongata. Peristalsis propels the bolus through the esophagus and toward the stomach. The circular muscle layer of the muscularis contracts, pinching

the esophageal wall and forcing the bolus forward. At the same time, the longitudinal muscle layer of the muscularis also contracts, shortening this area and pushing out its walls to receive the bolus. In this way, a series of contractions keeps moving food toward the stomach. When the bolus nears the stomach, distention of the esophagus initiates a short reflex relaxation of the lower esophageal sphincter that allows the bolus to pass into the stomach. During the esophageal phase, esophageal glands secrete mucus that lubricates the bolus and minimizes friction.

Note:

Watch this animation to see how swallowing is a complex process that involves the nervous system to coordinate the actions of upper respiratory and digestive activities. During which stage of swallowing is there a risk of food entering respiratory pathways and how is this risk blocked?

Chapter Review

In the mouth, the tongue and the teeth begin mechanical digestion, and saliva begins chemical digestion. The pharynx, which plays roles in breathing and vocalization as well as digestion, runs from the nasal and oral cavities superiorly to the esophagus inferiorly (for digestion) and to the larynx anteriorly (for respiration). During deglutition (swallowing), the soft palate rises to close off the nasopharynx, the larynx elevates, and the epiglottis folds over the glottis. The esophagus includes an upper esophageal sphincter made of skeletal muscle, which regulates the movement of food from the pharynx to the esophagus. It also has a lower esophageal sphincter, made of smooth muscle, which controls the passage

of food from the esophagus to the stomach. Cells in the esophageal wall secrete mucus that eases the passage of the food bolus.

Interactive Link Questions

Exercise:

Problem:

Watch this animation to see how swallowing is a complex process that involves the nervous system to coordinate the actions of upper respiratory and digestive activities. During which stage of swallowing is there a risk of food entering respiratory pathways and how is this risk blocked?

Solution:

Answers may vary.

Review Questions

Exercise:

Problem:

Which of these ingredients in saliva is responsible for activating salivary amylase?

a. mucus
b. phosphate ions
c. chloride ions
d. urea

Solution:

C

Exercise:

Problem: Which of these statements about the pharynx is true?

a. It extends from the nasal and oral cavities superiorly to the esophagus anteriorly.
b. The oropharynx is continuous superiorly with the nasopharynx.
c. The nasopharynx is involved in digestion.
d. The laryngopharynx is composed partially of cartilage.

Solution:

B

Exercise:

Problem:

Which structure is located where the esophagus penetrates the diaphragm?

a. esophageal hiatus
b. cardiac orifice
c. upper esophageal sphincter
d. lower esophageal sphincter

Solution:

A

Exercise:

Problem:

Which phase of deglutition involves contraction of the longitudinal muscle layer of the muscularis?

a. voluntary phase

b. buccal phase
c. pharyngeal phase
d. esophageal phase

Solution:

D

Critical Thinking Questions

Exercise:

Problem:

The composition of saliva varies from gland to gland. Discuss how saliva produced by the parotid gland differs in action from saliva produced by the sublingual gland.

Solution:

Parotid gland saliva is watery with little mucus but a lot of amylase, which allows it to mix freely with food during mastication and begin the digestion of carbohydrates. In contrast, sublingual gland saliva has a lot of mucus with the least amount of amylase of all the salivary glands. The high mucus content serves to lubricate the food for swallowing.

Exercise:

Problem:

During a hockey game, the puck hits a player in the mouth, knocking out all eight of his most anterior teeth. Which teeth did the player lose and how does this loss affect food ingestion?

Solution:

The incisors. Since these teeth are used for tearing off pieces of food during ingestion, the player will need to ingest foods that have already been cut into bite-sized pieces until the broken teeth are replaced.

Exercise:

Problem: What prevents swallowed food from entering the airways?

Solution:

Usually when food is swallowed, involuntary muscle contractions cause the soft palate to rise and close off the nasopharynx. The larynx also is pulled up, and the epiglottis folds over the glottis. These actions block off the air passages.

Exercise:

Problem:

Explain the mechanism responsible for gastroesophageal reflux.

Solution:

If the lower esophageal sphincter does not close completely, the stomach’s acidic contents can back up into the esophagus, a phenomenon known as GERD.

Exercise:

Problem:

Describe the three processes involved in the esophageal phase of deglutition.

Solution:

Peristalsis moves the bolus down the esophagus and toward the stomach. Esophageal glands secrete mucus that lubricates the bolus and reduces friction. When the bolus nears the stomach, the lower

esophageal sphincter relaxes, allowing the bolus to pass into the stomach.

References

van Loon FPL, Holmes SJ, Sirotkin B, Williams W, Cochi S, Hadler S, Lindegren ML. Morbidity and Mortality Weekly Report: Mumps surveillance -- United States, 1988–1993 [Internet]. Atlanta, GA: Center for Disease Control; [cited 2013 Apr 3]. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/00038546.htm.

Glossary

bolus
: mass of chewed food

cementum
: bone-like tissue covering the root of a tooth

crown
: portion of tooth visible superior to the gum line

cuspid
: (also, canine) pointed tooth used for tearing and shredding food

deciduous tooth
: one of 20 “baby teeth”

deglutition
: three-stage process of swallowing

dens
: tooth

dentin
: bone-like tissue immediately deep to the enamel of the crown or cementum of the root of a tooth

dentition
set of teeth

enamel
covering of the dentin of the crown of a tooth

esophagus
muscular tube that runs from the pharynx to the stomach

fauces
opening between the oral cavity and the oropharynx

gingiva
gum

incisor
midline, chisel-shaped tooth used for cutting into food

labium
lip

labial frenulum
midline mucous membrane fold that attaches the inner surface of the lips to the gums

laryngopharynx
part of the pharynx that functions in respiration and digestion

lingual frenulum
mucous membrane fold that attaches the bottom of the tongue to the floor of the mouth

lingual lipase
digestive enzyme from glands in the tongue that acts on triglycerides

lower esophageal sphincter
smooth muscle sphincter that regulates food movement from the esophagus to the stomach

molar
: tooth used for crushing and grinding food

oral cavity
: (also, buccal cavity) mouth

oral vestibule
: part of the mouth bounded externally by the cheeks and lips, and internally by the gums and teeth

oropharynx
: part of the pharynx continuous with the oral cavity that functions in respiration and digestion

palatoglossal arch
: muscular fold that extends from the lateral side of the soft palate to the base of the tongue

palatopharyngeal arch
: muscular fold that extends from the lateral side of the soft palate to the side of the pharynx

parotid gland
: one of a pair of major salivary glands located inferior and anterior to the ears

permanent tooth
: one of 32 adult teeth

pharynx
: throat

premolar
: (also, bicuspid) transitional tooth used for mastication, crushing, and grinding food

pulp cavity
: deepest portion of a tooth, containing nerve endings and blood vessels

root
: portion of a tooth embedded in the alveolar processes beneath the gum line

saliva
: aqueous solution of proteins and ions secreted into the mouth by the salivary glands

salivary amylase
: digestive enzyme in saliva that acts on starch

salivary gland
: an exocrine gland that secretes a digestive fluid called saliva

salivation
: secretion of saliva

soft palate
: posterior region of the bottom portion of the nasal cavity that consists of skeletal muscle

sublingual gland
: one of a pair of major salivary glands located beneath the tongue

submandibular gland
: one of a pair of major salivary glands located in the floor of the mouth

tongue
: accessory digestive organ of the mouth, the bulk of which is composed of skeletal muscle

upper esophageal sphincter
: skeletal muscle sphincter that regulates food movement from the pharynx to the esophagus

voluntary phase
: initial phase of deglutition, in which the bolus moves from the mouth to the oropharynx

The Stomach

By the end of this section, you will be able to:

- Label on a diagram the four main regions of the stomach, its curvatures, and its sphincter
- Identify the four main types of secreting cells in gastric glands, and their important products
- Explain why the stomach does not digest itself
- Describe the mechanical and chemical digestion of food entering the stomach

Although a minimal amount of carbohydrate digestion occurs in the mouth, chemical digestion really gets underway in the stomach. An expansion of the alimentary canal that lies immediately inferior to the esophagus, the stomach links the esophagus to the first part of the small intestine (the duodenum) and is relatively fixed in place at its esophageal and duodenal ends. In between, however, it can be a highly active structure, contracting and continually changing position and size. These contractions provide mechanical assistance to digestion. The empty stomach is only about the size of your fist, but can stretch to hold as much as 4 liters of food and fluid, or more than 75 times its empty volume, and then return to its resting size when empty. Although you might think that the size of a person’s stomach is related to how much food that individual consumes, body weight does not correlate with stomach size. Rather, when you eat greater quantities of food—such as at holiday dinner—you stretch the stomach more than when you eat less.

Popular culture tends to refer to the stomach as the location where all digestion takes place. Of course, this is not true. An important function of the stomach is to serve as a temporary holding chamber. You can ingest a meal far more quickly than it can be digested and absorbed by the small intestine. Thus, the stomach holds food and parses only small amounts into the small intestine at a time. Foods are not processed in the order they are eaten; rather, they are mixed together with digestive juices in the stomach until they are converted into chyme, which is released into the small intestine.

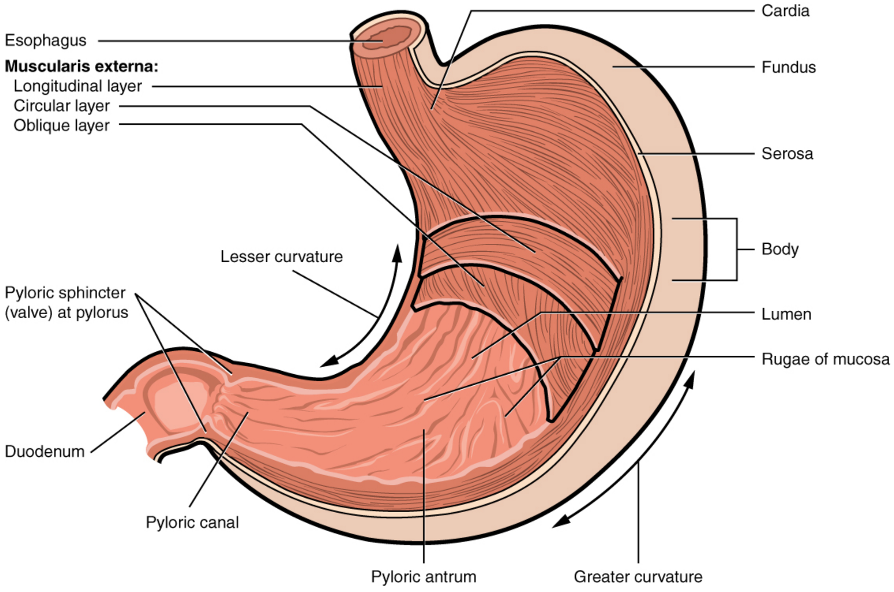
As you will see in the sections that follow, the stomach plays several important roles in chemical digestion, including the continued digestion of carbohydrates and the initial digestion of proteins and triglycerides. Little if any nutrient absorption occurs in the stomach, with the exception of the negligible amount of nutrients in alcohol.

Structure

There are four main regions in the **stomach**: the cardia, fundus, body, and pylorus ([link]). The **cardia** (or cardiac region) is the point where the esophagus connects to the stomach and through which food passes into the stomach. Located inferior to the diaphragm, above and to the left of the cardia, is the dome-shaped **fundus**. Below the fundus is the **body**, the main part of the stomach. The funnel-shaped **pylorus** connects the stomach to the duodenum. The wider end of the funnel, the **pyloric antrum**, connects

to the body of the stomach. The narrower end is called the **pyloric canal**, which connects to the duodenum. The smooth muscle **pyloric sphincter** is located at this latter point of connection and controls stomach emptying. In the absence of food, the stomach deflates inward, and its mucosa and submucosa fall into a large fold called a **ruga**.

Stomach



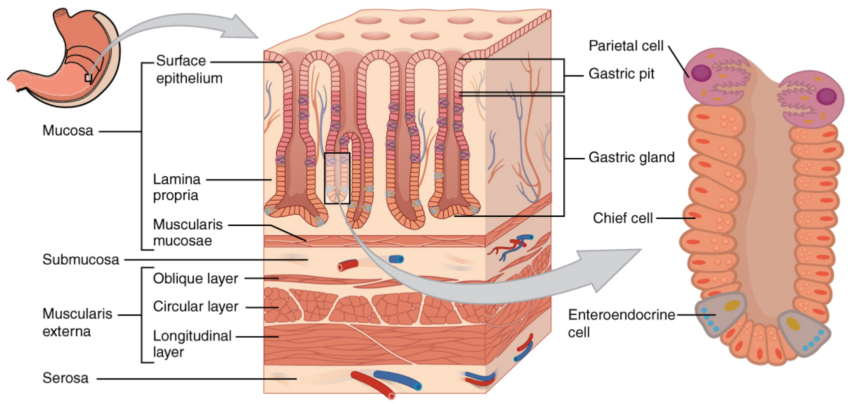
The stomach has four major regions: the cardia, fundus, body, and pylorus. The addition of an inner oblique smooth muscle layer gives the muscularis the ability to vigorously churn and mix food.

The convex lateral surface of the stomach is called the greater curvature; the concave medial border is the lesser curvature. The stomach is held in place by the lesser omentum, which extends from the liver to the lesser curvature, and the greater omentum, which runs from the greater curvature to the posterior abdominal wall.

Histology

The wall of the stomach is made of the same four layers as most of the rest of the alimentary canal, but with adaptations to the mucosa and muscularis for the unique functions of this organ. In addition to the typical circular and longitudinal smooth muscle layers, the muscularis has an inner oblique smooth muscle layer ([link]). As a result, in addition to moving food through the canal, the stomach can vigorously churn food, mechanically breaking it down into smaller particles.

Histology of the Stomach



The stomach wall is adapted for the functions of the stomach. In the epithelium, gastric pits lead to gastric glands that secrete gastric juice. The gastric glands (one gland is shown enlarged on the right) contain different types of cells that secrete a variety of enzymes, including hydrochloride acid, which activates the protein-digesting enzyme pepsin.

The stomach mucosa's epithelial lining consists only of surface mucus cells, which secrete a protective coat of alkaline mucus. A vast number of **gastric pits** dot the surface of the epithelium, giving it the appearance of a well-used pincushion, and mark the entry to each **gastric gland**, which secretes a complex digestive fluid referred to as gastric juice.

Although the walls of the gastric pits are made up primarily of mucus cells, the gastric glands are made up of different types of cells. The glands of the cardia and pylorus are composed primarily of mucus-secreting cells. Cells that make up the pyloric antrum secrete mucus and a number of hormones, including the majority of the stimulatory hormone, **gastrin**. The much larger glands of the fundus and body of the stomach, the site of most chemical digestion, produce most of the gastric secretions. These glands are made up of a variety of secretory cells. These include parietal cells, chief cells, mucous neck cells, and enteroendocrine cells.

Parietal cells—Located primarily in the middle region of the gastric glands are **parietal cells**, which are among the most highly differentiated of the body's epithelial cells. These relatively large cells produce both **hydrochloric acid (HCl)** and **intrinsic factor**. HCl is responsible for the high acidity (pH 1.5 to 3.5) of the stomach contents and is needed to activate the protein-digesting enzyme, pepsin. The acidity also kills much of the bacteria you ingest with food and helps to denature proteins, making them more available for enzymatic digestion. Intrinsic factor is a glycoprotein necessary for the absorption of vitamin B_{12} in the small intestine.

Chief cells—Located primarily in the basal regions of gastric glands are **chief cells**, which secrete **pepsinogen**, the inactive proenzyme form of pepsin. HCl is necessary for the conversion of pepsinogen to pepsin.

Mucous neck cells—Gastric glands in the upper part of the stomach contain **mucous neck cells** that secrete thin, acidic mucus that is much different from the mucus secreted by the goblet cells of the surface epithelium. The role of this mucus is not currently known.

Enteroendocrine cells—Finally, **enteroendocrine cells** found in the gastric glands secrete various hormones into the interstitial fluid of the lamina propria. These include gastrin, which is released mainly by enteroendocrine **G cells**.

[link] describes the digestive functions of important hormones secreted by the stomach.

Note:

Watch this animation that depicts the structure of the stomach and how this structure functions in the initiation of protein digestion. This view of the stomach shows the characteristic rugae. What is the function of these rugae?

Hormones Secreted by the Stomach

Hormone	Production site	Production stimulus	Target organ	Action

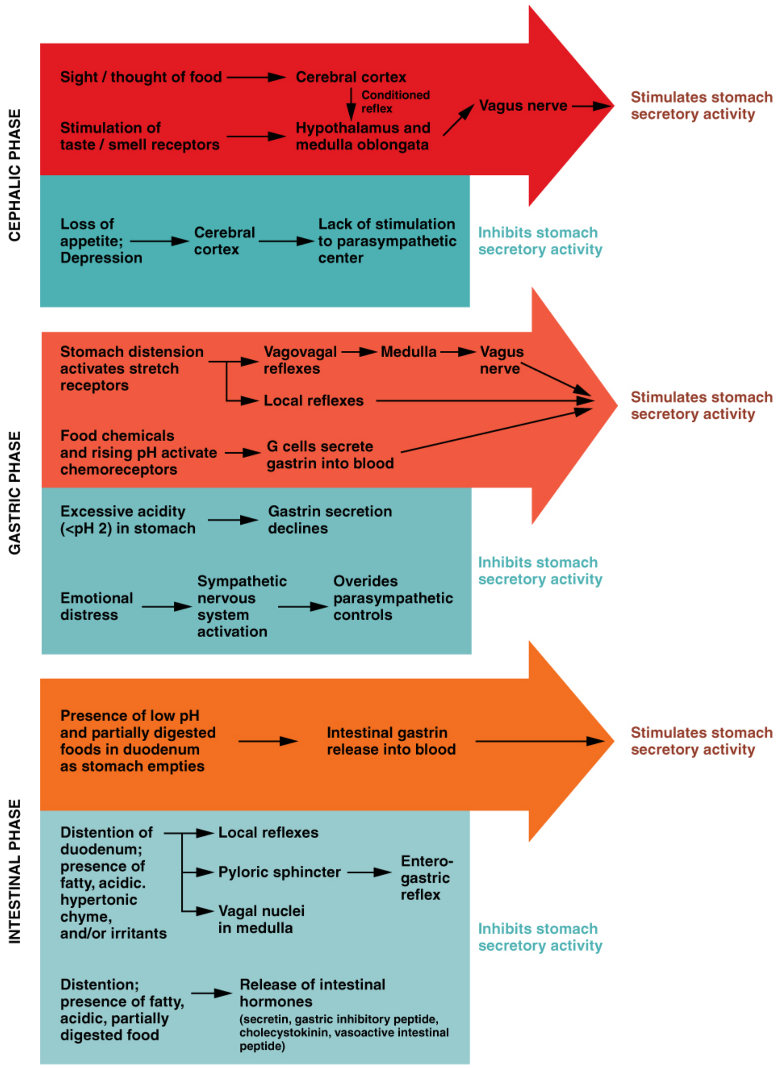
Hormones Secreted by the Stomach				
Hormone	**Production site**	**Production stimulus**	**Target organ**	**Action**
Gastrin	Stomach mucosa, mainly G cells of the pyloric antrum	Presence of peptides and amino acids in stomach	Stomach	Increases secretion by gastric glands; promotes gastric emptying
Gastrin	Stomach mucosa, mainly G cells of the pyloric antrum	Presence of peptides and amino acids in stomach	Small intestine	Promotes intestinal muscle contraction
Gastrin	Stomach mucosa, mainly G cells of the pyloric antrum	Presence of peptides and amino acids in stomach	Ileocecal valve	Relaxes valve
Gastrin	Stomach mucosa, mainly G cells of the pyloric antrum	Presence of peptides and amino acids in stomach	Large intestine	Triggers mass movements
Ghrelin	Stomach mucosa, mainly fundus	Fasting state (levels increase just prior to meals)	Hypothalamus	Regulates food intake, primarily by stimulating hunger and satiety

Hormones Secreted by the Stomach				
Hormone	**Production site**	**Production stimulus**	**Target organ**	**Action**
Histamine	Stomach mucosa	Presence of food in the stomach	Stomach	Stimulates parietal cells to release HCl
Serotonin	Stomach mucosa	Presence of food in the stomach	Stomach	Contracts stomach muscle
Somatostatin	Mucosa of stomach, especially pyloric antrum; also duodenum	Presence of food in the stomach; sympathetic axon stimulation	Stomach	Restricts all gastric secretions, gastric motility, and emptying
Somatostatin	Mucosa of stomach, especially pyloric antrum; also duodenum	Presence of food in the stomach; sympathetic axon stimulation	Pancreas	Restricts pancreatic secretions
Somatostatin	Mucosa of stomach, especially pyloric antrum; also duodenum	Presence of food in the stomach; sympathetic axon stimulation	Small intestine	Reduces intestinal absorption by reducing blood flow

Gastric Secretion

The secretion of gastric juice is controlled by both nerves and hormones. Stimuli in the brain, stomach, and small intestine activate or inhibit gastric juice production. This is why the three phases of gastric secretion are called the cephalic, gastric, and intestinal phases ([link]). However, once gastric secretion begins, all three phases can occur simultaneously.

The Three Phases of Gastric Secretion



Gastric secretion occurs in three phases: cephalic, gastric, and intestinal. During each phase, the secretion of gastric juice can be stimulated or inhibited.

The **cephalic phase** (reflex phase) of gastric secretion, which is relatively brief, takes place before food enters the stomach. The smell, taste, sight, or thought of food triggers

this phase. For example, when you bring a piece of sushi to your lips, impulses from receptors in your taste buds or the nose are relayed to your brain, which returns signals that increase gastric secretion to prepare your stomach for digestion. This enhanced secretion is a conditioned reflex, meaning it occurs only if you like or want a particular food. Depression and loss of appetite can suppress the cephalic reflex.

The **gastric phase** of secretion lasts 3 to 4 hours, and is set in motion by local neural and hormonal mechanisms triggered by the entry of food into the stomach. For example, when your sushi reaches the stomach, it creates distention that activates the stretch receptors. This stimulates parasympathetic neurons to release acetylcholine, which then provokes increased secretion of gastric juice. Partially digested proteins, caffeine, and rising pH stimulate the release of gastrin from enteroendocrine G cells, which in turn induces parietal cells to increase their production of HCl, which is needed to create an acidic environment for the conversion of pepsinogen to pepsin, and protein digestion. Additionally, the release of gastrin activates vigorous smooth muscle contractions. However, it should be noted that the stomach does have a natural means of avoiding excessive acid secretion and potential heartburn. Whenever pH levels drop too low, cells in the stomach react by suspending HCl secretion and increasing mucous secretions.

The **intestinal phase** of gastric secretion has both excitatory and inhibitory elements. The duodenum has a major role in regulating the stomach and its emptying. When partially digested food fills the duodenum, intestinal mucosal cells release a hormone called intestinal (enteric) gastrin, which further excites gastric juice secretion. This stimulatory activity is brief, however, because when the intestine distends with chyme, the enterogastric reflex inhibits secretion. One of the effects of this reflex is to close the pyloric sphincter, which blocks additional chyme from entering the duodenum.

The Mucosal Barrier

The mucosa of the stomach is exposed to the highly corrosive acidity of gastric juice. Gastric enzymes that can digest protein can also digest the stomach itself. The stomach is protected from self-digestion by the **mucosal barrier**. This barrier has several components. First, the stomach wall is covered by a thick coating of bicarbonate-rich mucus. This mucus forms a physical barrier, and its bicarbonate ions neutralize acid. Second, the epithelial cells of the stomach's mucosa meet at tight junctions, which block gastric juice from penetrating the underlying tissue layers. Finally, stem cells located where gastric glands join the gastric pits quickly replace damaged epithelial mucosal cells, when the epithelial cells are shed. In fact, the surface epithelium of the stomach is completely replaced every 3 to 6 days.

Note:
Homeostatic Imbalances

Ulcers: When the Mucosal Barrier Breaks Down
As effective as the mucosal barrier is, it is not a "fail-safe" mechanism. Sometimes, gastric juice eats away at the superficial lining of the stomach mucosa, creating erosions, which mostly heal on their own. Deeper and larger erosions are called ulcers.
Why does the mucosal barrier break down? A number of factors can interfere with its ability to protect the stomach lining. The majority of all ulcers are caused by either excessive intake of non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, or *Helicobacter pylori* infection.
Antacids help relieve symptoms of ulcers such as "burning" pain and indigestion. When ulcers are caused by NSAID use, switching to other classes of pain relievers allows healing. When caused by *H. pylori* infection, antibiotics are effective.
A potential complication of ulcers is perforation: Perforated ulcers create a hole in the stomach wall, resulting in peritonitis (inflammation of the peritoneum). These ulcers must be repaired surgically.

Digestive Functions of the Stomach

The stomach participates in virtually all the digestive activities with the exception of ingestion and defecation. Although almost all absorption takes place in the small intestine, the stomach does absorb some nonpolar substances, such as alcohol and aspirin.

Mechanical Digestion

Within a few moments after food after enters your stomach, mixing waves begin to occur at intervals of approximately 20 seconds. A **mixing wave** is a unique type of peristalsis that mixes and softens the food with gastric juices to create chyme. The initial mixing waves are relatively gentle, but these are followed by more intense waves, starting at the body of the stomach and increasing in force as they reach the pylorus. It is fair to say that long before your sushi exits through the pyloric sphincter, it bears little resemblance to the sushi you ate.

The pylorus, which holds around 30 mL (1 fluid ounce) of chyme, acts as a filter, permitting only liquids and small food particles to pass through the mostly, but not fully, closed pyloric sphincter. In a process called **gastric emptying**, rhythmic mixing waves force about 3 mL of chyme at a time through the pyloric sphincter and into the duodenum. Release of a greater amount of chyme at one time would overwhelm the capacity of the small intestine to handle it. The rest of the chyme is pushed back into the body of the stomach, where it continues mixing. This process is repeated when the next mixing waves force more chyme into the duodenum.

Gastric emptying is regulated by both the stomach and the duodenum. The presence of chyme in the duodenum activates receptors that inhibit gastric secretion. This prevents additional chyme from being released by the stomach before the duodenum is ready to process it.

Chemical Digestion

The fundus plays an important role, because it stores both undigested food and gases that are released during the process of chemical digestion. Food may sit in the fundus of the stomach for a while before being mixed with the chyme. While the food is in the fundus, the digestive activities of salivary amylase continue until the food begins mixing with the acidic chyme. Ultimately, mixing waves incorporate this food with the chyme, the acidity of which inactivates salivary amylase and activates lingual lipase. Lingual lipase then begins breaking down triglycerides into free fatty acids, and mono- and diglycerides.

The breakdown of protein begins in the stomach through the actions of HCl and the enzyme pepsin. During infancy, gastric glands also produce rennin, an enzyme that helps digest milk protein.

Its numerous digestive functions notwithstanding, there is only one stomach function necessary to life: the production of intrinsic factor. The intestinal absorption of vitamin B_{12}, which is necessary for both the production of mature red blood cells and normal neurological functioning, cannot occur without intrinsic factor. People who undergo total gastrectomy (stomach removal)—for life-threatening stomach cancer, for example—can survive with minimal digestive dysfunction if they receive vitamin B_{12} injections.

The contents of the stomach are completely emptied into the duodenum within 2 to 4 hours after you eat a meal. Different types of food take different amounts of time to process. Foods heavy in carbohydrates empty fastest, followed by high-protein foods. Meals with a high triglyceride content remain in the stomach the longest. Since enzymes in the small intestine digest fats slowly, food can stay in the stomach for 6 hours or longer when the duodenum is processing fatty chyme. However, note that this is still a fraction of the 24 to 72 hours that full digestion typically takes from start to finish.

Chapter Review

The stomach participates in all digestive activities except ingestion and defecation. It vigorously churns food. It secretes gastric juices that break down food and absorbs certain drugs, including aspirin and some alcohol. The stomach begins the digestion of protein and continues the digestion of carbohydrates and fats. It stores food as an acidic liquid called chyme, and releases it gradually into the small intestine through the pyloric sphincter.

Interactive Link Questions

Exercise:

Problem:

Watch this animation that depicts the structure of the stomach and how this structure functions in the initiation of protein digestion. This view of the stomach shows the characteristic rugae. What is the function of these rugae?

Solution:

Answers may vary.

Review Questions

Exercise:

Problem: Which of these cells secrete hormones?

a. parietal cells
b. mucous neck cells
c. enteroendocrine cells
d. chief cells

Solution:

C

Exercise:

Problem: Where does the majority of chemical digestion in the stomach occur?

a. fundus and body
b. cardia and fundus
c. body and pylorus
d. body

Solution:

A

Exercise:

Problem:

During gastric emptying, chyme is released into the duodenum through the ________.

a. esophageal hiatus
b. pyloric antrum
c. pyloric canal
d. pyloric sphincter

Solution:

D

Exercise:

Problem: Parietal cells secrete ________.

a. gastrin
b. hydrochloric acid
c. pepsin
d. pepsinogen

Solution:

B

Critical Thinking Questions

Exercise:

Problem:

Explain how the stomach is protected from self-digestion and why this is necessary.

Solution:

The mucosal barrier protects the stomach from self-digestion. It includes a thick coating of bicarbonate-rich mucus; the mucus is physically protective, and bicarbonate neutralizes gastric acid. Epithelial cells meet at tight junctions, which block gastric juice from penetrating the underlying tissue layers, and stem cells quickly replace sloughed off epithelial mucosal cells.

Exercise:

Problem:

Describe unique anatomical features that enable the stomach to perform digestive functions.

Solution:

The stomach has an additional inner oblique smooth muscle layer that helps the muscularis churn and mix food. The epithelium includes gastric glands that secrete gastric fluid. The gastric fluid consists mainly of mucous, HCl, and the enzyme pepsin released as pepsinogen.

Glossary

body
: mid-portion of the stomach

cardia
: (also, cardiac region) part of the stomach surrounding the cardiac orifice (esophageal hiatus)

cephalic phase
: (also, reflex phase) initial phase of gastric secretion that occurs before food enters the stomach

chief cell
: gastric gland cell that secretes pepsinogen

enteroendocrine cell
: gastric gland cell that releases hormones

fundus
: dome-shaped region of the stomach above and to the left of the cardia

G cell
: gastrin-secreting enteroendocrine cell

gastric emptying
: process by which mixing waves gradually cause the release of chyme into the duodenum

gastric gland
: gland in the stomach mucosal epithelium that produces gastric juice

gastric phase
: phase of gastric secretion that begins when food enters the stomach

gastric pit
: narrow channel formed by the epithelial lining of the stomach mucosa

gastrin
: peptide hormone that stimulates secretion of hydrochloric acid and gut motility

hydrochloric acid (HCl)
: digestive acid secreted by parietal cells in the stomach

intrinsic factor
: glycoprotein required for vitamin B_{12} absorption in the small intestine

intestinal phase
: phase of gastric secretion that begins when chyme enters the intestine

mixing wave
: unique type of peristalsis that occurs in the stomach

mucosal barrier
: protective barrier that prevents gastric juice from destroying the stomach itself

mucous neck cell
: gastric gland cell that secretes a uniquely acidic mucus

parietal cell
: gastric gland cell that secretes hydrochloric acid and intrinsic factor

pepsinogen
: inactive form of pepsin

pyloric antrum
: wider, more superior part of the pylorus

pyloric canal
: narrow, more inferior part of the pylorus

pyloric sphincter
: sphincter that controls stomach emptying

pylorus
: lower, funnel-shaped part of the stomach that is continuous with the duodenum

ruga

fold of alimentary canal mucosa and submucosa in the empty stomach and other organs

stomach
: alimentary canal organ that contributes to chemical and mechanical digestion of food from the esophagus before releasing it, as chyme, to the small intestine

The Small and Large Intestines
By the end of this section, you will be able to:

- Compare and contrast the location and gross anatomy of the small and large intestines
- Identify three main adaptations of the small intestine wall that increase its absorptive capacity
- Describe the mechanical and chemical digestion of chyme upon its release into the small intestine
- List three features unique to the wall of the large intestine and identify their contributions to its function
- Identify the beneficial roles of the bacterial flora in digestive system functioning
- Trace the pathway of food waste from its point of entry into the large intestine through its exit from the body as feces

The word intestine is derived from a Latin root meaning “internal,” and indeed, the two organs together nearly fill the interior of the abdominal cavity. In addition, called the small and large bowel, or colloquially the “guts,” they constitute the greatest mass and length of the alimentary canal and, with the exception of ingestion, perform all digestive system functions.

The Small Intestine

Chyme released from the stomach enters the **small intestine**, which is the primary digestive organ in the body. Not only is this where most digestion occurs, it is also where practically all absorption occurs. The longest part of the alimentary canal, the small intestine is about 3.05 meters (10 feet) long in a living person (but about twice as long in a cadaver due to the loss of muscle tone). Since this makes it about five times longer than the large intestine, you might wonder why it is called “small.” In fact, its name derives from its relatively smaller diameter of only about 2.54 cm (1 in), compared with 7.62 cm (3 in) for the large intestine. As we’ll see shortly, in addition to its length, the folds and projections of the lining of the small intestine work to give it an enormous surface area, which is approximately 200 m^2, more than 100 times the surface area of your skin. This large

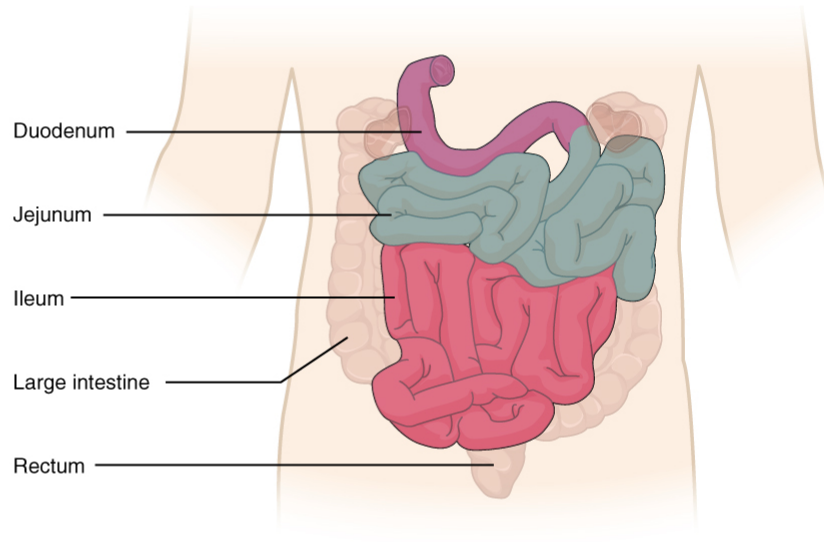
surface area is necessary for complex processes of digestion and absorption that occur within it.

Structure

The coiled tube of the small intestine is subdivided into three regions. From proximal (at the stomach) to distal, these are the duodenum, jejunum, and ileum ([link]).

The shortest region is the 25.4-cm (10-in) **duodenum**, which begins at the pyloric sphincter. Just past the pyloric sphincter, it bends posteriorly behind the peritoneum, becoming retroperitoneal, and then makes a C-shaped curve around the head of the pancreas before ascending anteriorly again to return to the peritoneal cavity and join the jejunum. The duodenum can therefore be subdivided into four segments: the superior, descending, horizontal, and ascending duodenum.

Of particular interest is the **hepatopancreatic ampulla** (ampulla of Vater). Located in the duodenal wall, the ampulla marks the transition from the anterior portion of the alimentary canal to the mid-region, and is where the bile duct (through which bile passes from the liver) and the **main pancreatic duct** (through which pancreatic juice passes from the pancreas) join. This ampulla opens into the duodenum at a tiny volcano-shaped structure called the **major duodenal papilla**. The **hepatopancreatic sphincter** (sphincter of Oddi) regulates the flow of both bile and pancreatic juice from the ampulla into the duodenum.
Small Intestine



The three regions of the small intestine are the duodenum, jejunum, and ileum.

The **jejunum** is about 0.9 meters (3 feet) long (in life) and runs from the duodenum to the ileum. Jejunum means “empty” in Latin and supposedly was so named by the ancient Greeks who noticed it was always empty at death. No clear demarcation exists between the jejunum and the final segment of the small intestine, the ileum.

The **ileum** is the longest part of the small intestine, measuring about 1.8 meters (6 feet) in length. It is thicker, more vascular, and has more developed mucosal folds than the jejunum. The ileum joins the cecum, the first portion of the large intestine, at the **ileocecal sphincter** (or valve). The jejunum and ileum are tethered to the posterior abdominal wall by the mesentery. The large intestine frames these three parts of the small intestine.

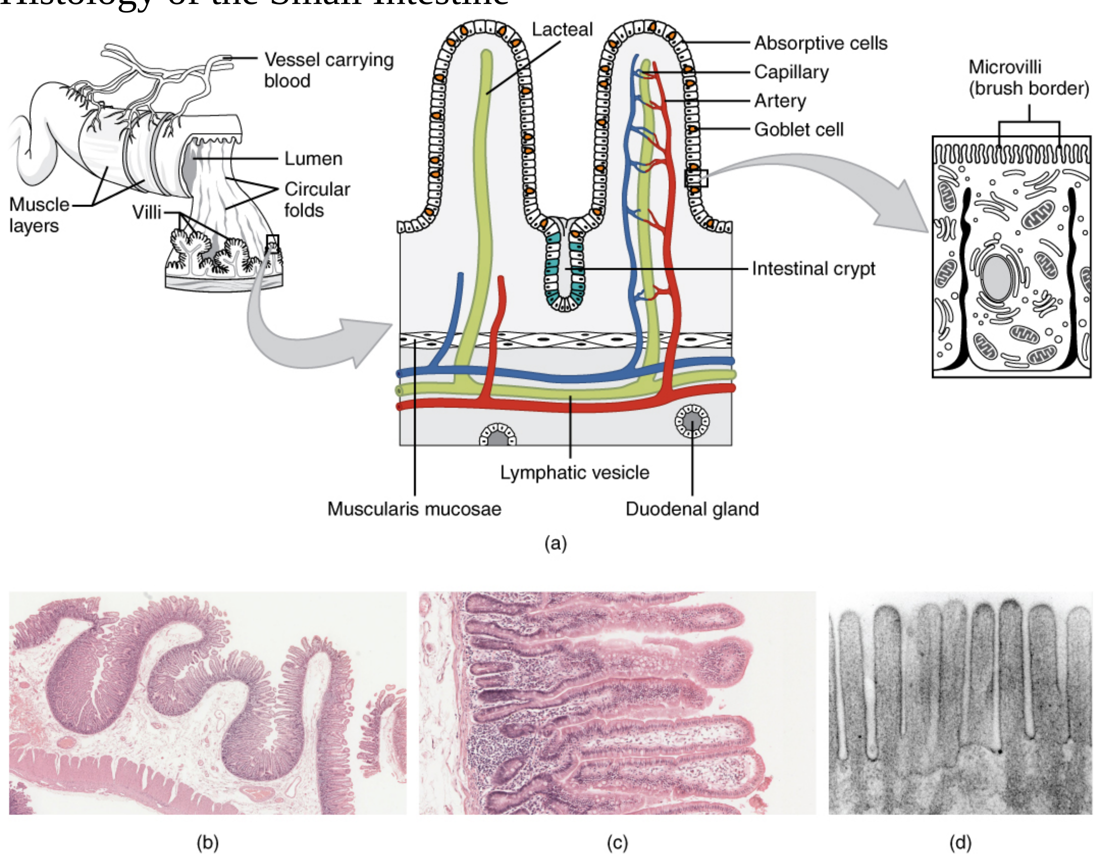
Parasympathetic nerve fibers from the vagus nerve and sympathetic nerve fibers from the thoracic splanchnic nerve provide extrinsic innervation to the small intestine. The superior mesenteric artery is its main arterial supply. Veins run parallel to the arteries and drain into the superior

mesenteric vein. Nutrient-rich blood from the small intestine is then carried to the liver via the hepatic portal vein.

Histology

The wall of the small intestine is composed of the same four layers typically present in the alimentary system. However, three features of the mucosa and submucosa are unique. These features, which increase the absorptive surface area of the small intestine more than 600-fold, include circular folds, villi, and microvilli ([link]). These adaptations are most abundant in the proximal two-thirds of the small intestine, where the majority of absorption occurs.

Histology of the Small Intestine



(a) The absorptive surface of the small intestine is vastly enlarged by the presence of circular folds, villi, and microvilli. (b) Micrograph of the circular folds. (c) Micrograph of the villi.

(d) Electron micrograph of the microvilli. From left to right, LM x 56, LM x 508, EM x 196,000. (credit b-d: Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Circular folds

Also called a plica circulare, a **circular fold** is a deep ridge in the mucosa and submucosa. Beginning near the proximal part of the duodenum and ending near the middle of the ileum, these folds facilitate absorption. Their shape causes the chyme to spiral, rather than move in a straight line, through the small intestine. Spiraling slows the movement of chyme and provides the time needed for nutrients to be fully absorbed.

Villi

Within the circular folds are small (0.5–1 mm long) hairlike vascularized projections called **villi** (singular = villus) that give the mucosa a furry texture. There are about 20 to 40 villi per square millimeter, increasing the surface area of the epithelium tremendously. The mucosal epithelium, primarily composed of absorptive cells, covers the villi. In addition to muscle and connective tissue to support its structure, each villus contains a capillary bed composed of one arteriole and one venule, as well as a lymphatic capillary called a **lacteal**. The breakdown products of carbohydrates and proteins (sugars and amino acids) can enter the bloodstream directly, but lipid breakdown products are absorbed by the lacteals and transported to the bloodstream via the lymphatic system.

Microvilli

As their name suggests, **microvilli** (singular = microvillus) are much smaller (1 μm) than villi. They are cylindrical apical surface extensions of the plasma membrane of the mucosa's epithelial cells, and are supported by microfilaments within those cells. Although their small size makes it difficult to see each microvillus, their combined microscopic appearance suggests a mass of bristles, which is termed the **brush border**. Fixed to the surface of the microvilli membranes are enzymes that finish digesting carbohydrates and proteins. There are an estimated 200 million microvilli per square millimeter of small intestine, greatly expanding the surface area of the plasma membrane and thus greatly enhancing absorption.

Intestinal Glands

In addition to the three specialized absorptive features just discussed, the mucosa between the villi is dotted with deep crevices that each lead into a tubular **intestinal gland** (crypt of Lieberkühn), which is formed by cells that line the crevices (see [link]). These produce **intestinal juice**, a slightly alkaline (pH 7.4 to 7.8) mixture of water and mucus. Each day, about 0.95 to 1.9 liters (1 to 2 quarts) are secreted in response to the distention of the small intestine or the irritating effects of chyme on the intestinal mucosa.

The submucosa of the duodenum is the only site of the complex mucus-secreting **duodenal glands** (Brunner's glands), which produce a bicarbonate-rich alkaline mucus that buffers the acidic chyme as it enters from the stomach.

The roles of the cells in the small intestinal mucosa are detailed in [link].

Cells of the Small Intestinal Mucosa

Cells of the Small Intestinal Mucosa

Cell type | Location in the mucosa | Function

Cell type	Location in the mucosa	Function
Absorptive	Epithelium/intestinal glands	Digestion and absorption of nutrients in chyme
Goblet	Epithelium/intestinal glands	Secretion of mucus
Paneth	Intestinal glands	Secretion of the bactericidal enzyme lysozyme; phagocytosis
G cells	Intestinal glands of duodenum	Secretion of the hormone intestinal gastrin
I cells	Intestinal glands of duodenum	Secretion of the hormone cholecystokinin, which stimulates release of pancreatic juices and bile
K cells	Intestinal glands	Secretion of the hormone glucose-dependent insulinotropic peptide, which stimulates the release of insulin

Cells of the Small Intestinal Mucosa

Cell type	**Location in the mucosa**	**Function**
M cells	Intestinal glands of duodenum and jejunum	Secretion of the hormone motilin, which accelerates gastric emptying, stimulates intestinal peristalsis, and stimulates the production of pepsin
S cells	Intestinal glands	Secretion of the hormone secretin

Intestinal MALT

The lamina propria of the small intestine mucosa is studded with quite a bit of MALT. In addition to solitary lymphatic nodules, aggregations of intestinal MALT, which are typically referred to as Peyer’s patches, are concentrated in the distal ileum, and serve to keep bacteria from entering the bloodstream. Peyer’s patches are most prominent in young people and become less distinct as you age, which coincides with the general activity of our immune system.

Note:

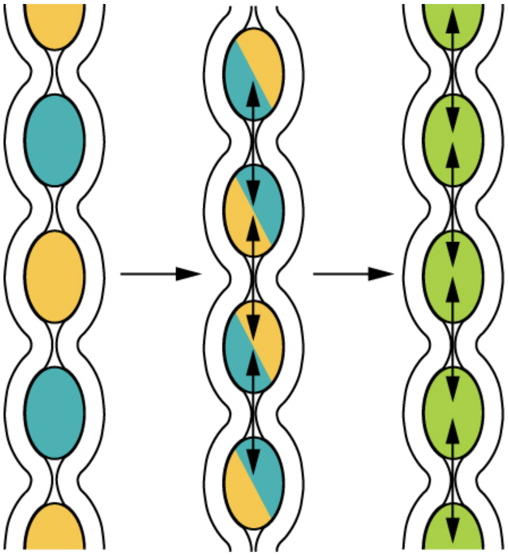
Watch this animation that depicts the structure of the small intestine, and, in particular, the villi. Epithelial cells continue the digestion and absorption of nutrients and transport these nutrients to the lymphatic and circulatory systems. In the small intestine, the products of food digestion are absorbed by different structures in the villi. Which structure absorbs and transports fats?

Mechanical Digestion in the Small Intestine

The movement of intestinal smooth muscles includes both segmentation and a form of peristalsis called migrating motility complexes. The kind of peristaltic mixing waves seen in the stomach are not observed here.

If you could see into the small intestine when it was going through segmentation, it would look as if the contents were being shoved incrementally back and forth, as the rings of smooth muscle repeatedly contract and then relax. Segmentation in the small intestine does not force chyme through the tract. Instead, it combines the chyme with digestive juices and pushes food particles against the mucosa to be absorbed. The duodenum is where the most rapid segmentation occurs, at a rate of about 12 times per minute. In the ileum, segmentations are only about eight times per minute ([link]).

Segmentation



Segmentation separates chyme and then pushes it back together, mixing it and providing time for digestion and absorption.

When most of the chyme has been absorbed, the small intestinal wall becomes less distended. At this point, the localized segmentation process is replaced by transport movements. The duodenal mucosa secretes the hormone **motilin**, which initiates peristalsis in the form of a **migrating motility complex**. These complexes, which begin in the duodenum, force chyme through a short section of the small intestine and then stop. The next contraction begins a little bit farther down than the first, forces chyme a bit farther through the small intestine, then stops. These complexes move slowly down the small intestine, forcing chyme on the way, taking around 90 to 120 minutes to finally reach the end of the ileum. At this point, the process is repeated, starting in the duodenum.

The ileocecal valve, a sphincter, is usually in a constricted state, but when motility in the ileum increases, this sphincter relaxes, allowing food residue to enter the first portion of the large intestine, the cecum. Relaxation of the ileocecal sphincter is controlled by both nerves and hormones. First,

digestive activity in the stomach provokes the **gastroileal reflex**, which increases the force of ileal segmentation. Second, the stomach releases the hormone gastrin, which enhances ileal motility, thus relaxing the ileocecal sphincter. After chyme passes through, backward pressure helps close the sphincter, preventing backflow into the ileum. Because of this reflex, your lunch is completely emptied from your stomach and small intestine by the time you eat your dinner. It takes about 3 to 5 hours for all chyme to leave the small intestine.

Chemical Digestion in the Small Intestine

The digestion of proteins and carbohydrates, which partially occurs in the stomach, is completed in the small intestine with the aid of intestinal and pancreatic juices. Lipids arrive in the intestine largely undigested, so much of the focus here is on lipid digestion, which is facilitated by bile and the enzyme pancreatic lipase.

Moreover, intestinal juice combines with pancreatic juice to provide a liquid medium that facilitates absorption. The intestine is also where most water is absorbed, via osmosis. The small intestine’s absorptive cells also synthesize digestive enzymes and then place them in the plasma membranes of the microvilli. This distinguishes the small intestine from the stomach; that is, enzymatic digestion occurs not only in the lumen, but also on the luminal surfaces of the mucosal cells.

For optimal chemical digestion, chyme must be delivered from the stomach slowly and in small amounts. This is because chyme from the stomach is typically hypertonic, and if large quantities were forced all at once into the small intestine, the resulting osmotic water loss from the blood into the intestinal lumen would result in potentially life-threatening low blood volume. In addition, continued digestion requires an upward adjustment of the low pH of stomach chyme, along with rigorous mixing of the chyme with bile and pancreatic juices. Both processes take time, so the pumping action of the pylorus must be carefully controlled to prevent the duodenum from being overwhelmed with chyme.

Note:

Disorders of the…

Small Intestine: Lactose Intolerance

Lactose intolerance is a condition characterized by indigestion caused by dairy products. It occurs when the absorptive cells of the small intestine do not produce enough lactase, the enzyme that digests the milk sugar lactose. In most mammals, lactose intolerance increases with age. In contrast, some human populations, most notably Caucasians, are able to maintain the ability to produce lactase as adults.

In people with lactose intolerance, the lactose in chyme is not digested. Bacteria in the large intestine ferment the undigested lactose, a process that produces gas. In addition to gas, symptoms include abdominal cramps, bloating, and diarrhea. Symptom severity ranges from mild discomfort to severe pain; however, symptoms resolve once the lactose is eliminated in feces.

The hydrogen breath test is used to help diagnose lactose intolerance. Lactose-tolerant people have very little hydrogen in their breath. Those with lactose intolerance exhale hydrogen, which is one of the gases produced by the bacterial fermentation of lactose in the colon. After the hydrogen is absorbed from the intestine, it is transported through blood vessels into the lungs. There are a number of lactose-free dairy products available in grocery stores. In addition, dietary supplements are available. Taken with food, they provide lactase to help digest lactose.

The Large Intestine

The **large intestine** is the terminal part of the alimentary canal. The primary function of this organ is to finish absorption of nutrients and water, synthesize certain vitamins, form feces, and eliminate feces from the body.

Structure

The large intestine runs from the appendix to the anus. It frames the small intestine on three sides. Despite its being about one-half as long as the small

intestine, it is called large because it is more than twice the diameter of the small intestine, about 3 inches.

Subdivisions

The large intestine is subdivided into four main regions: the cecum, the colon, the rectum, and the anus. The ileocecal valve, located at the opening between the ileum and the large intestine, controls the flow of chyme from the small intestine to the large intestine.

Cecum

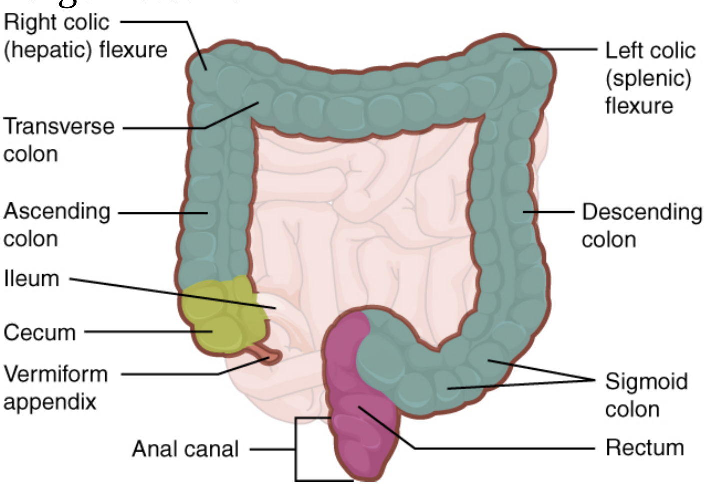
The first part of the large intestine is the **cecum**, a sac-like structure that is suspended inferior to the ileocecal valve. It is about 6 cm (2.4 in) long, receives the contents of the ileum, and continues the absorption of water and salts. The **appendix** (or vermiform appendix) is a winding tube that attaches to the cecum. Although the 7.6-cm (3-in) long appendix contains lymphoid tissue, suggesting an immunologic function, this organ is generally considered vestigial. However, at least one recent report postulates a survival advantage conferred by the appendix: In diarrheal illness, the appendix may serve as a bacterial reservoir to repopulate the enteric bacteria for those surviving the initial phases of the illness. Moreover, its twisted anatomy provides a haven for the accumulation and multiplication of enteric bacteria. The **mesoappendix**, the mesentery of the appendix, tethers it to the mesentery of the ileum.

Colon

The cecum blends seamlessly with the **colon**. Upon entering the colon, the food residue first travels up the **ascending colon** on the right side of the abdomen. At the inferior surface of the liver, the colon bends to form the **right colic flexure** (hepatic flexure) and becomes the **transverse colon**. The region defined as hindgut begins with the last third of the transverse

colon and continues on. Food residue passing through the transverse colon travels across to the left side of the abdomen, where the colon angles sharply immediately inferior to the spleen, at the **left colic flexure** (splenic flexure). From there, food residue passes through the **descending colon**, which runs down the left side of the posterior abdominal wall. After entering the pelvis inferiorly, it becomes the s-shaped **sigmoid colon**, which extends medially to the midline ([link]). The ascending and descending colon, and the rectum (discussed next) are located in the retroperitoneum. The transverse and sigmoid colon are tethered to the posterior abdominal wall by the mesocolon.

Large Intestine



The large intestine includes the cecum, colon, and rectum.

Note:

Homeostatic Imbalances

Colorectal Cancer

Each year, approximately 140,000 Americans are diagnosed with colorectal cancer, and another 49,000 die from it, making it one of the most deadly malignancies. People with a family history of colorectal cancer are at increased risk. Smoking, excessive alcohol consumption, and a diet high in animal fat and protein also increase the risk. Despite popular opinion to

the contrary, studies support the conclusion that dietary fiber and calcium do not reduce the risk of colorectal cancer.
Colorectal cancer may be signaled by constipation or diarrhea, cramping, abdominal pain, and rectal bleeding. Bleeding from the rectum may be either obvious or occult (hidden in feces). Since most colon cancers arise from benign mucosal growths called polyps, cancer prevention is focused on identifying these polyps. The colonoscopy is both diagnostic and therapeutic. Colonoscopy not only allows identification of precancerous polyps, the procedure also enables them to be removed before they become malignant. Screening for fecal occult blood tests and colonoscopy is recommended for those over 50 years of age.

Rectum

Food residue leaving the sigmoid colon enters the **rectum** in the pelvis, near the third sacral vertebra. The final 20.3 cm (8 in) of the alimentary canal, the rectum extends anterior to the sacrum and coccyx. Even though rectum is Latin for “straight,” this structure follows the curved contour of the sacrum and has three lateral bends that create a trio of internal transverse folds called the **rectal valves**. These valves help separate the feces from gas to prevent the simultaneous passage of feces and gas.

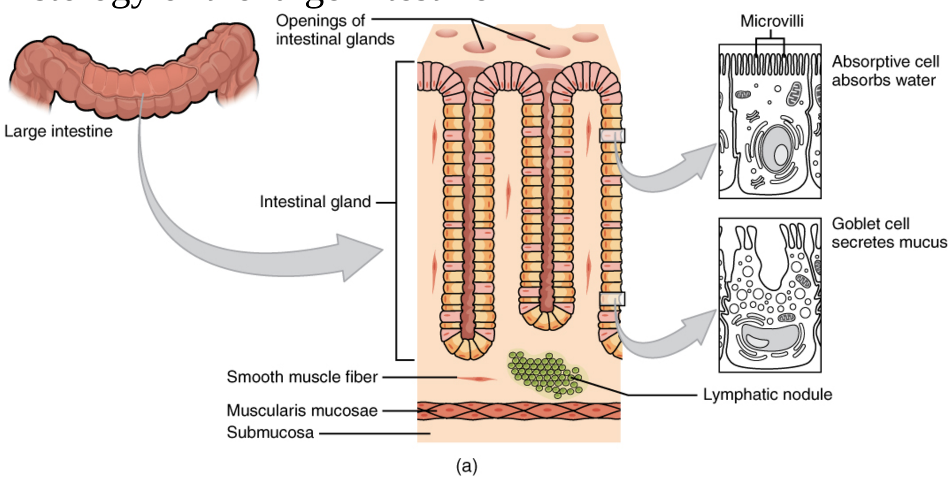
Anal Canal

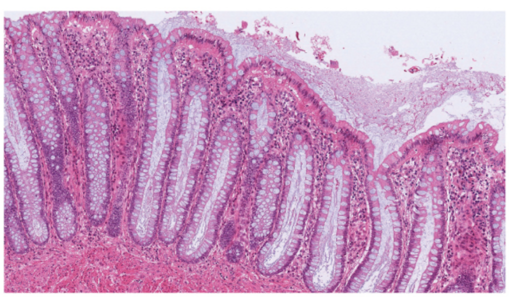
Finally, food residue reaches the last part of the large intestine, the **anal canal**, which is located in the perineum, completely outside of the abdominopelvic cavity. This 3.8–5 cm (1.5–2 in) long structure opens to the exterior of the body at the anus. The anal canal includes two sphincters. The **internal anal sphincter** is made of smooth muscle, and its contractions are involuntary. The **external anal sphincter** is made of skeletal muscle, which is under voluntary control. Except when defecating, both usually remain closed.

Histology

There are several notable differences between the walls of the large and small intestines ([link]). For example, few enzyme-secreting cells are found in the wall of the large intestine, and there are no circular folds or villi. Other than in the anal canal, the mucosa of the colon is simple columnar epithelium made mostly of enterocytes (absorptive cells) and goblet cells. In addition, the wall of the large intestine has far more intestinal glands, which contain a vast population of enterocytes and goblet cells. These goblet cells secrete mucus that eases the movement of feces and protects the intestine from the effects of the acids and gases produced by enteric bacteria. The enterocytes absorb water and salts as well as vitamins produced by your intestinal bacteria.

Histology of the large Intestine





(b)

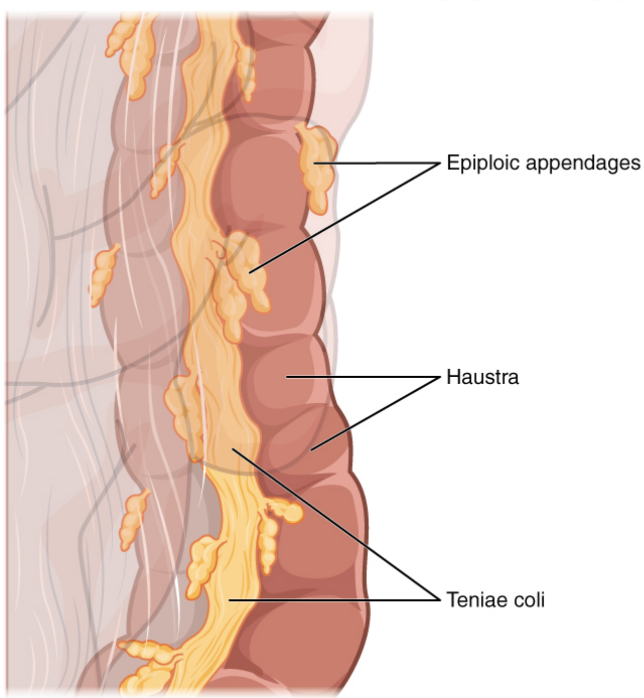
(a) The histologies of the large intestine and small intestine (not shown) are adapted for the digestive functions of each organ. (b) This micrograph shows the colon's simple columnar epithelium and goblet

cells. LM x 464. (credit b: Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Anatomy

Three features are unique to the large intestine: teniae coli, haustra, and epiploic appendages ([link]). The **teniae coli** are three bands of smooth muscle that make up the longitudinal muscle layer of the muscularis of the large intestine, except at its terminal end. Tonic contractions of the teniae coli bunch up the colon into a succession of pouches called **haustra** (singular = haustrum), which are responsible for the wrinkled appearance of the colon. Attached to the teniae coli are small, fat-filled sacs of visceral peritoneum called **epiploic appendages**. The purpose of these is unknown. Although the rectum and anal canal have neither teniae coli nor haustra, they do have well-developed layers of muscularis that create the strong contractions needed for defecation.

Teniae Coli, Haustra, and Epiploic Appendages



The stratified squamous epithelial mucosa of the anal canal connects to the skin on the outside of the anus. This mucosa varies considerably from that of the rest of the colon to accommodate the high level of abrasion as feces pass through. The anal canal's mucous membrane is organized into longitudinal folds, each called an **anal column**, which house a grid of arteries and veins. Two superficial venous plexuses are found in the anal canal: one within the anal columns and one at the anus.

Depressions between the anal columns, each called an **anal sinus**, secrete mucus that facilitates defecation. The **pectinate line** (or dentate line) is a horizontal, jagged band that runs circumferentially just below the level of the anal sinuses, and represents the junction between the hindgut and external skin. The mucosa above this line is fairly insensitive, whereas the area below is very sensitive. The resulting difference in pain threshold is due to the fact that the upper region is innervated by visceral sensory fibers, and the lower region is innervated by somatic sensory fibers.

Bacterial Flora

Most bacteria that enter the alimentary canal are killed by lysozyme, defensins, HCl, or protein-digesting enzymes. However, trillions of bacteria live within the large intestine and are referred to as the **bacterial flora**. Most of the more than 700 species of these bacteria are nonpathogenic commensal organisms that cause no harm as long as they stay in the gut lumen. In fact, many facilitate chemical digestion and absorption, and some synthesize certain vitamins, mainly biotin, pantothenic acid, and vitamin K. Some are linked to increased immune response. A refined system prevents these bacteria from crossing the mucosal barrier. First, peptidoglycan, a component of bacterial cell walls, activates the release of chemicals by the mucosa's epithelial cells, which draft immune cells, especially dendritic cells, into the mucosa. Dendritic cells open the tight junctions between epithelial cells and extend probes into the lumen to evaluate the microbial antigens. The dendritic cells with antigens then travel to neighboring lymphoid follicles in the mucosa where T cells inspect for antigens. This process triggers an IgA-mediated response, if warranted, in the lumen that

blocks the commensal organisms from infiltrating the mucosa and setting off a far greater, widespread systematic reaction.

Digestive Functions of the Large Intestine

The residue of chyme that enters the large intestine contains few nutrients except water, which is reabsorbed as the residue lingers in the large intestine, typically for 12 to 24 hours. Thus, it may not surprise you that the large intestine can be completely removed without significantly affecting digestive functioning. For example, in severe cases of inflammatory bowel disease, the large intestine can be removed by a procedure known as a colectomy. Often, a new fecal pouch can be crafted from the small intestine and sutured to the anus, but if not, an ileostomy can be created by bringing the distal ileum through the abdominal wall, allowing the watery chyme to be collected in a bag-like adhesive appliance.

Mechanical Digestion

In the large intestine, mechanical digestion begins when chyme moves from the ileum into the cecum, an activity regulated by the ileocecal sphincter. Right after you eat, peristalsis in the ileum forces chyme into the cecum. When the cecum is distended with chyme, contractions of the ileocecal sphincter strengthen. Once chyme enters the cecum, colon movements begin.

Mechanical digestion in the large intestine includes a combination of three types of movements. The presence of food residues in the colon stimulates a slow-moving **haustral contraction**. This type of movement involves sluggish segmentation, primarily in the transverse and descending colons. When a haustrum is distended with chyme, its muscle contracts, pushing the residue into the next haustrum. These contractions occur about every 30 minutes, and each last about 1 minute. These movements also mix the food residue, which helps the large intestine absorb water. The second type of movement is peristalsis, which, in the large intestine, is slower than in the more proximal portions of the alimentary canal. The third type is a **mass**

movement. These strong waves start midway through the transverse colon and quickly force the contents toward the rectum. Mass movements usually occur three or four times per day, either while you eat or immediately afterward. Distension in the stomach and the breakdown products of digestion in the small intestine provoke the **gastrocolic reflex**, which increases motility, including mass movements, in the colon. Fiber in the diet both softens the stool and increases the power of colonic contractions, optimizing the activities of the colon.

Chemical Digestion

Although the glands of the large intestine secrete mucus, they do not secrete digestive enzymes. Therefore, chemical digestion in the large intestine occurs exclusively because of bacteria in the lumen of the colon. Through the process of **saccharolytic fermentation**, bacteria break down some of the remaining carbohydrates. This results in the discharge of hydrogen, carbon dioxide, and methane gases that create **flatus** (gas) in the colon; flatulence is excessive flatus. Each day, up to 1500 mL of flatus is produced in the colon. More is produced when you eat foods such as beans, which are rich in otherwise indigestible sugars and complex carbohydrates like soluble dietary fiber.

Absorption, Feces Formation, and Defecation

The small intestine absorbs about 90 percent of the water you ingest (either as liquid or within solid food). The large intestine absorbs most of the remaining water, a process that converts the liquid chyme residue into semisolid **feces** (“stool”). Feces is composed of undigested food residues, unabsorbed digested substances, millions of bacteria, old epithelial cells from the GI mucosa, inorganic salts, and enough water to let it pass smoothly out of the body. Of every 500 mL (17 ounces) of food residue that enters the cecum each day, about 150 mL (5 ounces) become feces.

Feces are eliminated through contractions of the rectal muscles. You help this process by a voluntary procedure called **Valsalva’s maneuver**, in

which you increase intra-abdominal pressure by contracting your diaphragm and abdominal wall muscles, and closing your glottis.

The process of defecation begins when mass movements force feces from the colon into the rectum, stretching the rectal wall and provoking the defecation reflex, which eliminates feces from the rectum. This parasympathetic reflex is mediated by the spinal cord. It contracts the sigmoid colon and rectum, relaxes the internal anal sphincter, and initially contracts the external anal sphincter. The presence of feces in the anal canal sends a signal to the brain, which gives you the choice of voluntarily opening the external anal sphincter (defecating) or keeping it temporarily closed. If you decide to delay defecation, it takes a few seconds for the reflex contractions to stop and the rectal walls to relax. The next mass movement will trigger additional defecation reflexes until you defecate.

If defecation is delayed for an extended time, additional water is absorbed, making the feces firmer and potentially leading to constipation. On the other hand, if the waste matter moves too quickly through the intestines, not enough water is absorbed, and diarrhea can result. This can be caused by the ingestion of foodborne pathogens. In general, diet, health, and stress determine the frequency of bowel movements. The number of bowel movements varies greatly between individuals, ranging from two or three per day to three or four per week.

Note:

By watching this animation you will see that for the various food groups—proteins, fats, and carbohydrates—digestion begins in different parts of the digestion system, though all end in the same place. Of the three major food

classes (carbohydrates, fats, and proteins), which is digested in the mouth, the stomach, and the small intestine?

Chapter Review

The three main regions of the small intestine are the duodenum, the jejunum, and the ileum. The small intestine is where digestion is completed and virtually all absorption occurs. These two activities are facilitated by structural adaptations that increase the mucosal surface area by 600-fold, including circular folds, villi, and microvilli. There are around 200 million microvilli per square millimeter of small intestine, which contain brush border enzymes that complete the digestion of carbohydrates and proteins. Combined with pancreatic juice, intestinal juice provides the liquid medium needed to further digest and absorb substances from chyme. The small intestine is also the site of unique mechanical digestive movements. Segmentation moves the chyme back and forth, increasing mixing and opportunities for absorption. Migrating motility complexes propel the residual chyme toward the large intestine.

The main regions of the large intestine are the cecum, the colon, and the rectum. The large intestine absorbs water and forms feces, and is responsible for defecation. Bacterial flora break down additional carbohydrate residue, and synthesize certain vitamins. The mucosa of the large intestinal wall is generously endowed with goblet cells, which secrete mucus that eases the passage of feces. The entry of feces into the rectum activates the defecation reflex.

Interactive Link Questions

Exercise:

Problem:

Watch this animation that depicts the structure of the small intestine, and, in particular, the villi. Epithelial cells continue the digestion and absorption of nutrients and transport these nutrients to the lymphatic and circulatory systems. In the small intestine, the products of food digestion are absorbed by different structures in the villi. Which structure absorbs and transports fats?

Solution:

Answers may vary.

Exercise:

Problem:

By watching this animation, you will see that for the various food groups—proteins, fats, and carbohydrates—digestion begins in different parts of the digestion system, though all end in the same place. Of the three major food classes (carbohydrates, fats, and proteins), which is digested in the mouth, the stomach, and the small intestine?

Solution:

Answers may vary.

Review Questions

Exercise:

Problem:

In which part of the alimentary canal does most digestion occur?

a. stomach
b. proximal small intestine

c. distal small intestine
d. ascending colon

Solution:

B

Exercise:

Problem: Which of these is most associated with villi?

a. haustra
b. lacteals
c. bacterial flora
d. intestinal glands

Solution:

B

Exercise:

Problem: What is the role of the small intestine's MALT?

a. secreting mucus
b. buffering acidic chyme
c. activating pepsin
d. preventing bacteria from entering the bloodstream

Solution:

D

Exercise:

Problem: Which part of the large intestine attaches to the appendix?

a. cecum
b. ascending colon
c. transverse colon
d. descending colon

Solution:

A

Critical Thinking Questions

Exercise:

Problem:

Explain how nutrients absorbed in the small intestine pass into the general circulation.

Solution:

Nutrients from the breakdown of carbohydrates and proteins are absorbed through a capillary bed in the villi of the small intestine. Lipid breakdown products are absorbed into a lacteal in the villi, and transported via the lymphatic system to the bloodstream.

Exercise:

Problem:

Why is it important that chyme from the stomach is delivered to the small intestine slowly and in small amounts?

Solution:

If large quantities of chyme were forced into the small intestine, it would result in osmotic water loss from the blood into the intestinal lumen that could cause potentially life-threatening low blood volume and erosion of the duodenum.

Exercise:

Problem:

Describe three of the differences between the walls of the large and small intestines.

Solution:

The mucosa of the small intestine includes circular folds, villi, and microvilli. The wall of the large intestine has a thick mucosal layer, and deeper and more abundant mucus-secreting glands that facilitate the smooth passage of feces. There are three features that are unique to the large intestine: teniae coli, haustra, and epiploic appendages.

References

American Cancer Society (US). Cancer facts and figures: colorectal cancer: 2011–2013 [Internet]. c2013 [cited 2013 Apr 3]. Available from: http://www.cancer.org/Research/CancerFactsFigures/ColorectalCancerFactsFigures/colorectal-cancer-facts-figures-2011-2013-page.

The Nutrition Source. Fiber and colon cancer: following the scientific trail [Internet]. Boston (MA): Harvard School of Public Health; c2012 [cited 2013 Apr 3]. Available from: http://www.hsph.harvard.edu/nutritionsource/nutrition-news/fiber-and-colon-cancer/index.html.

Centers for Disease Control and Prevention (US). Morbidity and mortality weekly report: notifiable diseases and mortality tables [Internet]. Atlanta (GA); [cited 2013 Apr 3]. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6101md.htm?s_cid=mm6101md_w.

Glossary

anal canal

final segment of the large intestine

anal column
: long fold of mucosa in the anal canal

anal sinus
: recess between anal columns

appendix
: (vermiform appendix) coiled tube attached to the cecum

ascending colon
: first region of the colon

bacterial flora
: bacteria in the large intestine

brush border
: fuzzy appearance of the small intestinal mucosa created by microvilli

cecum
: pouch forming the beginning of the large intestine

circular fold
: (also, plica circulare) deep fold in the mucosa and submucosa of the small intestine

colon
: part of the large intestine between the cecum and the rectum

descending colon
: part of the colon between the transverse colon and the sigmoid colon

duodenal gland
: (also, Brunner’s gland) mucous-secreting gland in the duodenal submucosa

duodenum

first part of the small intestine, which starts at the pyloric sphincter and ends at the jejunum

epiploic appendage
small sac of fat-filled visceral peritoneum attached to teniae coli

external anal sphincter
voluntary skeletal muscle sphincter in the anal canal

feces
semisolid waste product of digestion

flatus
gas in the intestine

gastrocolic reflex
propulsive movement in the colon activated by the presence of food in the stomach

gastroileal reflex
long reflex that increases the strength of segmentation in the ileum

haustrum
small pouch in the colon created by tonic contractions of teniae coli

haustral contraction
slow segmentation in the large intestine

hepatopancreatic ampulla
(also, ampulla of Vater) bulb-like point in the wall of the duodenum where the bile duct and main pancreatic duct unite

hepatopancreatic sphincter
(also, sphincter of Oddi) sphincter regulating the flow of bile and pancreatic juice into the duodenum

ileocecal sphincter
sphincter located where the small intestine joins with the large intestine

ileum
: end of the small intestine between the jejunum and the large intestine

internal anal sphincter
: involuntary smooth muscle sphincter in the anal canal

intestinal gland
: (also, crypt of Lieberkühn) gland in the small intestinal mucosa that secretes intestinal juice

intestinal juice
: mixture of water and mucus that helps absorb nutrients from chyme

jejunum
: middle part of the small intestine between the duodenum and the ileum

lacteal
: lymphatic capillary in the villi

large intestine
: terminal portion of the alimentary canal

left colic flexure
: (also, splenic flexure) point where the transverse colon curves below the inferior end of the spleen

main pancreatic duct
: (also, duct of Wirsung) duct through which pancreatic juice drains from the pancreas

major duodenal papilla
: point at which the hepatopancreatic ampulla opens into the duodenum

mass movement
: long, slow, peristaltic wave in the large intestine

mesoappendix
: mesentery of the appendix

microvillus
small projection of the plasma membrane of the absorptive cells of the small intestinal mucosa

migrating motility complex
form of peristalsis in the small intestine

motilin
hormone that initiates migrating motility complexes

pectinate line
horizontal line that runs like a ring, perpendicular to the inferior margins of the anal sinuses

rectal valve
one of three transverse folds in the rectum where feces is separated from flatus

rectum
part of the large intestine between the sigmoid colon and anal canal

right colic flexure
(also, hepatic flexure) point, at the inferior surface of the liver, where the ascending colon turns abruptly to the left

saccharolytic fermentation
anaerobic decomposition of carbohydrates

sigmoid colon
end portion of the colon, which terminates at the rectum

small intestine
section of the alimentary canal where most digestion and absorption occurs

tenia coli
one of three smooth muscle bands that make up the longitudinal muscle layer of the muscularis in all of the large intestine except the

terminal end

transverse colon
: part of the colon between the ascending colon and the descending colon

Valsalva’s maneuver
: voluntary contraction of the diaphragm and abdominal wall muscles and closing of the glottis, which increases intra-abdominal pressure and facilitates defecation

villus
: projection of the mucosa of the small intestine

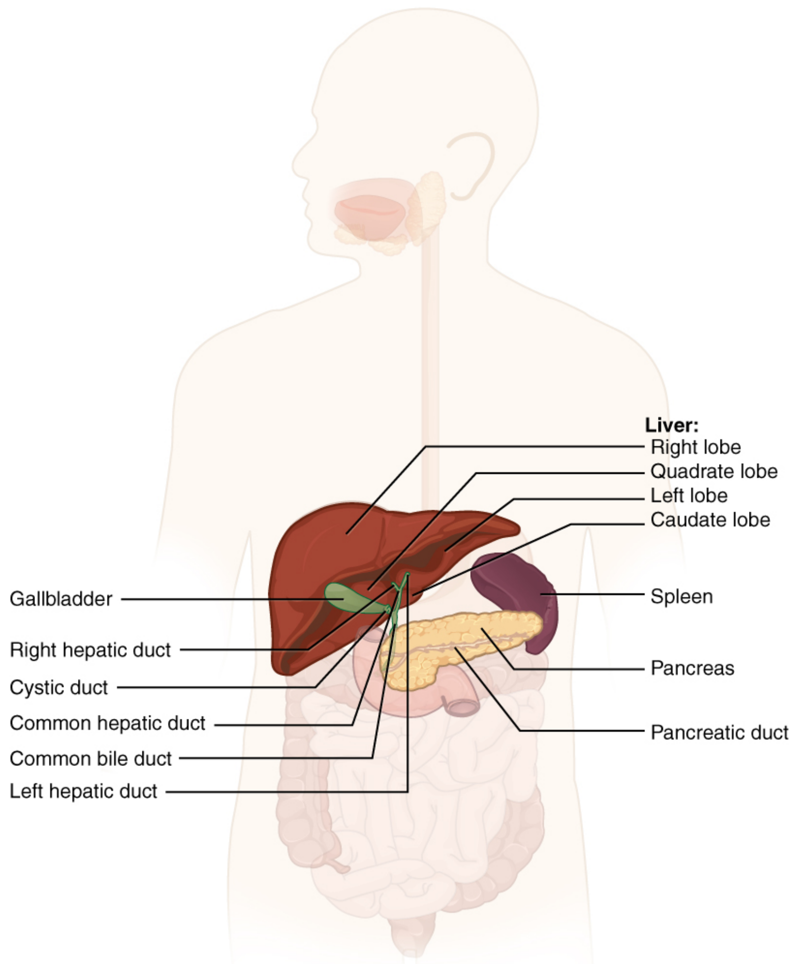
Accessory Organs in Digestion: The Liver, Pancreas, and Gallbladder

By the end of this section, you will be able to:

- State the main digestive roles of the liver, pancreas, and gallbladder
- Identify three main features of liver histology that are critical to its function
- Discuss the composition and function of bile
- Identify the major types of enzymes and buffers present in pancreatic juice

Chemical digestion in the small intestine relies on the activities of three accessory digestive organs: the liver, pancreas, and gallbladder ([link]). The digestive role of the liver is to produce bile and export it to the duodenum. The gallbladder primarily stores, concentrates, and releases bile. The pancreas produces pancreatic juice, which contains digestive enzymes and bicarbonate ions, and delivers it to the duodenum.

Accessory Organs



The liver, pancreas, and gallbladder are considered accessory digestive organs, but their roles in the digestive system are vital.

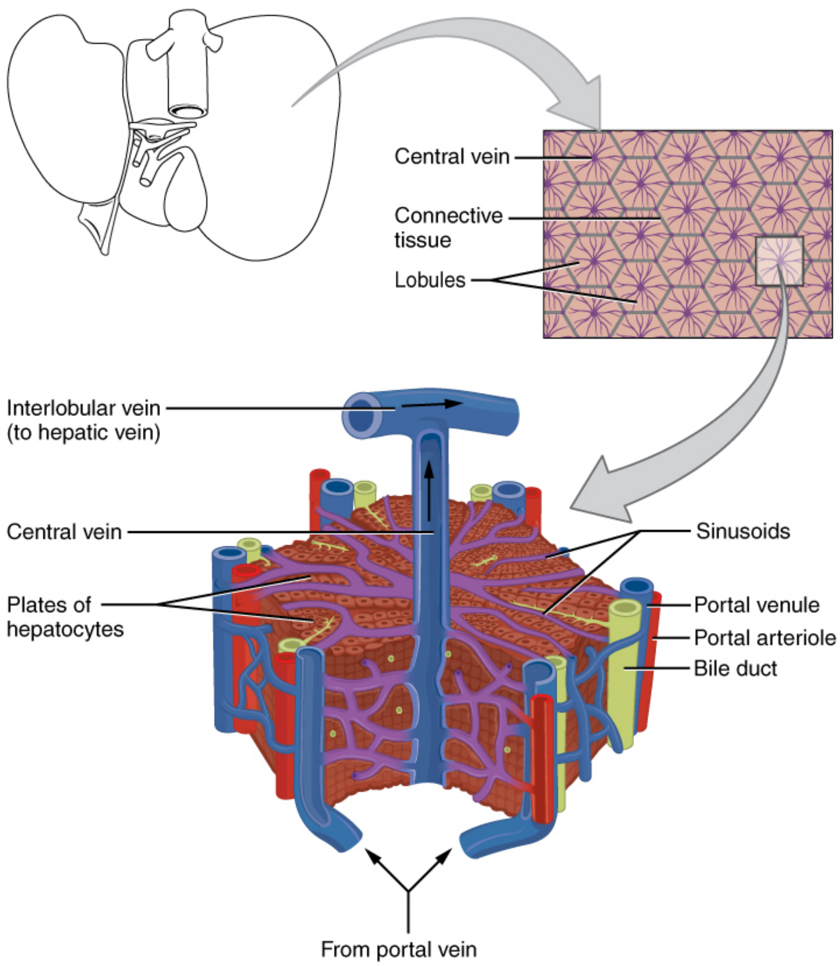
The Liver

The **liver** is the largest gland in the body, weighing about three pounds in an adult. It is also one of the most important organs. In addition to being an accessory digestive organ, it plays a number of roles in metabolism and regulation. The liver lies inferior to the diaphragm in the right upper quadrant of the abdominal cavity and receives protection from the surrounding ribs.

The liver is divided into two primary lobes: a large right lobe and a much smaller left lobe. In the right lobe, some anatomists also identify an inferior quadrate lobe and a posterior caudate lobe, which are defined by internal features. The liver is connected to the abdominal wall and diaphragm by five peritoneal folds referred to as ligaments. These are the falciform ligament, the coronary ligament, two lateral ligaments, and the ligamentum teres hepatis. The falciform ligament and ligamentum teres hepatis are actually remnants of the umbilical vein, and separate the right and left lobes anteriorly. The lesser omentum tethers the liver to the lesser curvature of the stomach.

The **porta hepatis** (“gate to the liver”) is where the **hepatic artery** and **hepatic portal vein** enter the liver. These two vessels, along with the common hepatic duct, run behind the lateral border of the lesser omentum on the way to their destinations. As shown in [link], the hepatic artery delivers oxygenated blood from the heart to the liver. The hepatic portal vein delivers partially deoxygenated blood containing nutrients absorbed from the small intestine and actually supplies more oxygen to the liver than do the much smaller hepatic arteries. In addition to nutrients, drugs and toxins are also absorbed. After processing the bloodborne nutrients and toxins, the liver releases nutrients needed by other cells back into the blood, which drains into the central vein and then through the hepatic vein to the inferior vena cava. With this hepatic portal circulation, all blood from the alimentary canal passes through the liver. This largely explains why the liver is the most common site for the metastasis of cancers that originate in the alimentary canal.

Microscopic Anatomy of the Liver



The liver receives oxygenated blood from the hepatic artery and nutrient-rich deoxygenated blood from the hepatic portal vein.

Histology

The liver has three main components: hepatocytes, bile canaliculi, and hepatic sinusoids. A **hepatocyte** is the liver’s main cell type, accounting for around 80 percent of the liver's volume. These cells play a role in a wide variety of secretory, metabolic, and endocrine functions. Plates of

hepatocytes called hepatic laminae radiate outward from the portal vein in each **hepatic lobule**.

Between adjacent hepatocytes, grooves in the cell membranes provide room for each **bile canaliculus** (plural = canaliculi). These small ducts accumulate the bile produced by hepatocytes. From here, bile flows first into bile ductules and then into bile ducts. The bile ducts unite to form the larger right and left hepatic ducts, which themselves merge and exit the liver as the **common hepatic duct**. This duct then joins with the cystic duct from the gallbladder, forming the **common bile duct** through which bile flows into the small intestine.

A **hepatic sinusoid** is an open, porous blood space formed by fenestrated capillaries from nutrient-rich hepatic portal veins and oxygen-rich hepatic arteries. Hepatocytes are tightly packed around the fenestrated endothelium of these spaces, giving them easy access to the blood. From their central position, hepatocytes process the nutrients, toxins, and waste materials carried by the blood. Materials such as bilirubin are processed and excreted into the bile canaliculi. Other materials including proteins, lipids, and carbohydrates are processed and secreted into the sinusoids or just stored in the cells until called upon. The hepatic sinusoids combine and send blood to a **central vein**. Blood then flows through a **hepatic vein** into the inferior vena cava. This means that blood and bile flow in opposite directions. The hepatic sinusoids also contain star-shaped **reticuloendothelial cells** (Kupffer cells), phagocytes that remove dead red and white blood cells, bacteria, and other foreign material that enter the sinusoids. The **portal triad** is a distinctive arrangement around the perimeter of hepatic lobules, consisting of three basic structures: a bile duct, a hepatic artery branch, and a hepatic portal vein branch.

Bile

Recall that lipids are hydrophobic, that is, they do not dissolve in water. Thus, before they can be digested in the watery environment of the small intestine, large lipid globules must be broken down into smaller lipid

globules, a process called emulsification. **Bile** is a mixture secreted by the liver to accomplish the emulsification of lipids in the small intestine.

Hepatocytes secrete about one liter of bile each day. A yellow-brown or yellow-green alkaline solution (pH 7.6 to 8.6), bile is a mixture of water, bile salts, bile pigments, phospholipids (such as lecithin), electrolytes, cholesterol, and triglycerides. The components most critical to emulsification are bile salts and phospholipids, which have a nonpolar (hydrophobic) region as well as a polar (hydrophilic) region. The hydrophobic region interacts with the large lipid molecules, whereas the hydrophilic region interacts with the watery chyme in the intestine. This results in the large lipid globules being pulled apart into many tiny lipid fragments of about 1 μm in diameter. This change dramatically increases the surface area available for lipid-digesting enzyme activity. This is the same way dish soap works on fats mixed with water.

Bile salts act as emulsifying agents, so they are also important for the absorption of digested lipids. While most constituents of bile are eliminated in feces, bile salts are reclaimed by the **enterohepatic circulation**. Once bile salts reach the ileum, they are absorbed and returned to the liver in the hepatic portal blood. The hepatocytes then excrete the bile salts into newly formed bile. Thus, this precious resource is recycled.

Bilirubin, the main bile pigment, is a waste product produced when the spleen removes old or damaged red blood cells from the circulation. These breakdown products, including proteins, iron, and toxic bilirubin, are transported to the liver via the splenic vein of the hepatic portal system. In the liver, proteins and iron are recycled, whereas bilirubin is excreted in the bile. It accounts for the green color of bile. Bilirubin is eventually transformed by intestinal bacteria into stercobilin, a brown pigment that gives your stool its characteristic color! In some disease states, bile does not enter the intestine, resulting in white (‘acholic’) stool with a high fat content, since virtually no fats are broken down or absorbed.

Hepatocytes work non-stop, but bile production increases when fatty chyme enters the duodenum and stimulates the secretion of the gut hormone secretin. Between meals, bile is produced but conserved. The valve-like

hepatopancreatic ampulla closes, allowing bile to divert to the gallbladder, where it is concentrated and stored until the next meal.

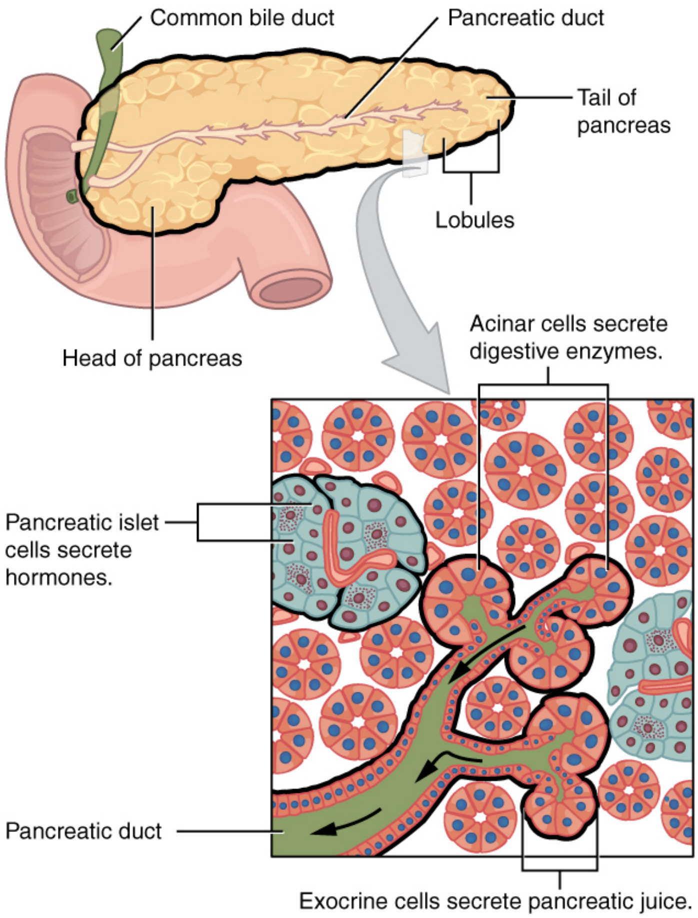
Note:

Watch this video to see the structure of the liver and how this structure supports the functions of the liver, including the processing of nutrients, toxins, and wastes. At rest, about 1500 mL of blood per minute flow through the liver. What percentage of this blood flow comes from the hepatic portal system?

The Pancreas

The soft, oblong, glandular **pancreas** lies transversely in the retroperitoneum behind the stomach. Its head is nestled into the “c-shaped” curvature of the duodenum with the body extending to the left about 15.2 cm (6 in) and ending as a tapering tail in the hilum of the spleen. It is a curious mix of exocrine (secreting digestive enzymes) and endocrine (releasing hormones into the blood) functions ([link]).

Exocrine and Endocrine Pancreas



The pancreas has a head, a body, and a tail. It delivers pancreatic juice to the duodenum through the pancreatic duct.

The exocrine part of the pancreas arises as little grape-like cell clusters, each called an **acinus** (plural = acini), located at the terminal ends of pancreatic ducts. These acinar cells secrete enzyme-rich **pancreatic juice** into tiny merging ducts that form two dominant ducts. The larger duct fuses with the common bile duct (carrying bile from the liver and gallbladder) just before entering the duodenum via a common opening (the hepatopancreatic ampulla). The smooth muscle sphincter of the hepatopancreatic ampulla controls the release of pancreatic juice and bile into the small intestine. The second and smaller pancreatic duct, the

accessory duct (duct of Santorini), runs from the pancreas directly into the duodenum, approximately 1 inch above the hepatopancreatic ampulla. When present, it is a persistent remnant of pancreatic development.

Scattered through the sea of exocrine acini are small islands of endocrine cells, the islets of Langerhans. These vital cells produce the hormones pancreatic polypeptide, insulin, glucagon, and somatostatin.

Pancreatic Juice

The pancreas produces over a liter of pancreatic juice each day. Unlike bile, it is clear and composed mostly of water along with some salts, sodium bicarbonate, and several digestive enzymes. Sodium bicarbonate is responsible for the slight alkalinity of pancreatic juice (pH 7.1 to 8.2), which serves to buffer the acidic gastric juice in chyme, inactivate pepsin from the stomach, and create an optimal environment for the activity of pH-sensitive digestive enzymes in the small intestine. Pancreatic enzymes are active in the digestion of sugars, proteins, and fats.

The pancreas produces protein-digesting enzymes in their inactive forms. These enzymes are activated in the duodenum. If produced in an active form, they would digest the pancreas (which is exactly what occurs in the disease, pancreatitis). The intestinal brush border enzyme **enteropeptidase** stimulates the activation of trypsin from trypsinogen of the pancreas, which in turn changes the pancreatic enzymes procarboxypeptidase and chymotrypsinogen into their active forms, carboxypeptidase and chymotrypsin.

The enzymes that digest starch (amylase), fat (lipase), and nucleic acids (nuclease) are secreted in their active forms, since they do not attack the pancreas as do the protein-digesting enzymes.

Pancreatic Secretion

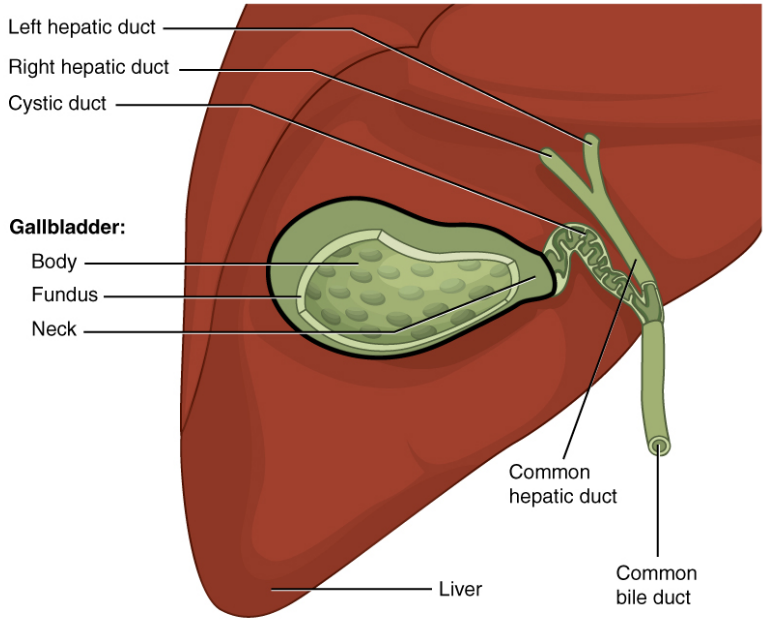
Regulation of pancreatic secretion is the job of hormones and the parasympathetic nervous system. The entry of acidic chyme into the duodenum stimulates the release of secretin, which in turn causes the duct cells to release bicarbonate-rich pancreatic juice. The presence of proteins and fats in the duodenum stimulates the secretion of CCK, which then stimulates the acini to secrete enzyme-rich pancreatic juice and enhances the activity of secretin. Parasympathetic regulation occurs mainly during the cephalic and gastric phases of gastric secretion, when vagal stimulation prompts the secretion of pancreatic juice.

Usually, the pancreas secretes just enough bicarbonate to counterbalance the amount of HCl produced in the stomach. Hydrogen ions enter the blood when bicarbonate is secreted by the pancreas. Thus, the acidic blood draining from the pancreas neutralizes the alkaline blood draining from the stomach, maintaining the pH of the venous blood that flows to the liver.

The Gallbladder

The **gallbladder** is 8–10 cm (~3–4 in) long and is nested in a shallow area on the posterior aspect of the right lobe of the liver. This muscular sac stores, concentrates, and, when stimulated, propels the bile into the duodenum via the common bile duct. It is divided into three regions. The fundus is the widest portion and tapers medially into the body, which in turn narrows to become the neck. The neck angles slightly superiorly as it approaches the hepatic duct. The cystic duct is 1–2 cm (less than 1 in) long and turns inferiorly as it bridges the neck and hepatic duct.

The simple columnar epithelium of the gallbladder mucosa is organized in rugae, similar to those of the stomach. There is no submucosa in the gallbladder wall. The wall’s middle, muscular coat is made of smooth muscle fibers. When these fibers contract, the gallbladder’s contents are ejected through the **cystic duct** and into the bile duct ([link]). Visceral peritoneum reflected from the liver capsule holds the gallbladder against the liver and forms the outer coat of the gallbladder. The gallbladder's mucosa absorbs water and ions from bile, concentrating it by up to 10-fold.
Gallbladder



The gallbladder stores and concentrates bile, and releases it into the two-way cystic duct when it is needed by the small intestine.

Chapter Review

Chemical digestion in the small intestine cannot occur without the help of the liver and pancreas. The liver produces bile and delivers it to the common hepatic duct. Bile contains bile salts and phospholipids, which emulsify large lipid globules into tiny lipid droplets, a necessary step in lipid digestion and absorption. The gallbladder stores and concentrates bile, releasing it when it is needed by the small intestine.

The pancreas produces the enzyme- and bicarbonate-rich pancreatic juice and delivers it to the small intestine through ducts. Pancreatic juice buffers the acidic gastric juice in chyme, inactivates pepsin from the stomach, and enables the optimal functioning of digestive enzymes in the small intestine.

Interactive Link Questions

Exercise:

Problem:

Watch this video to see the structure of the liver and how this structure supports the functions of the liver, including the processing of nutrients, toxins, and wastes. At rest, about 1500 mL of blood per minute flow through the liver. What percentage of this blood flow comes from the hepatic portal system?

Solution:

Answers may vary.

Review Questions

Exercise:

Problem: Which of these statements about bile is true?

a. About 500 mL is secreted daily.
b. Its main function is the denaturation of proteins.
c. It is synthesized in the gallbladder.
d. Bile salts are recycled.

Solution:

D

Exercise:

Problem: Pancreatic juice ________.

a. deactivates bile.
b. is secreted by pancreatic islet cells.
c. buffers chyme.
d. is released into the cystic duct.

Solution:

C

Critical Thinking Questions

Exercise:

Problem:

Why does the pancreas secrete some enzymes in their inactive forms, and where are these enzymes activated?

Solution:

The pancreas secretes protein-digesting enzymes in their inactive forms. If secreted in their active forms, they would self-digest the pancreas. These enzymes are activated in the duodenum.

Exercise:

Problem:

Describe the location of hepatocytes in the liver and how this arrangement enhances their function.

Solution:

The hepatocytes are the main cell type of the liver. They process, store, and release nutrients into the blood. Radiating out from the central vein, they are tightly packed around the hepatic sinusoids, allowing the hepatocytes easy access to the blood flowing through the sinusoids.

Glossary

accessory duct

(also, duct of Santorini) duct that runs from the pancreas into the duodenum

acinus
cluster of glandular epithelial cells in the pancreas that secretes pancreatic juice in the pancreas

bile
alkaline solution produced by the liver and important for the emulsification of lipids

bile canaliculus
small duct between hepatocytes that collects bile

bilirubin
main bile pigment, which is responsible for the brown color of feces

central vein
vein that receives blood from hepatic sinusoids

common bile duct
structure formed by the union of the common hepatic duct and the gallbladder’s cystic duct

common hepatic duct
duct formed by the merger of the two hepatic ducts

cystic duct
duct through which bile drains and enters the gallbladder

enterohepatic circulation
recycling mechanism that conserves bile salts

enteropeptidase
intestinal brush-border enzyme that activates trypsinogen to trypsin

gallbladder
accessory digestive organ that stores and concentrates bile

hepatic artery
artery that supplies oxygenated blood to the liver

hepatic lobule
hexagonal-shaped structure composed of hepatocytes that radiate outward from a central vein

hepatic portal vein
vein that supplies deoxygenated nutrient-rich blood to the liver

hepatic sinusoid
blood capillaries between rows of hepatocytes that receive blood from the hepatic portal vein and the branches of the hepatic artery

hepatic vein
vein that drains into the inferior vena cava

hepatocytes
major functional cells of the liver

liver
largest gland in the body whose main digestive function is the production of bile

pancreas
accessory digestive organ that secretes pancreatic juice

pancreatic juice
secretion of the pancreas containing digestive enzymes and bicarbonate

porta hepatis
“gateway to the liver” where the hepatic artery and hepatic portal vein enter the liver

portal triad
bile duct, hepatic artery branch, and hepatic portal vein branch

reticuloendothelial cell

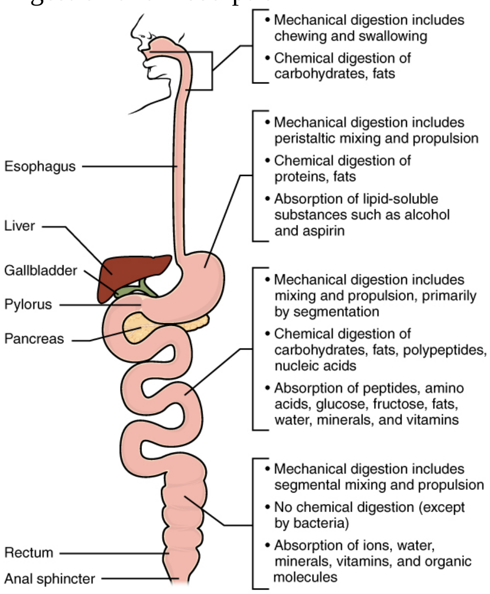
(also, Kupffer cell) phagocyte in hepatic sinusoids that filters out material from venous blood from the alimentary canal

Chemical Digestion and Absorption: A Closer Look
By the end of this section, you will be able to:

- Identify the locations and primary secretions involved in the chemical digestion of carbohydrates, proteins, lipids, and nucleic acids
- Compare and contrast absorption of the hydrophilic and hydrophobic nutrients

As you have learned, the process of mechanical digestion is relatively simple. It involves the physical breakdown of food but does not alter its chemical makeup. Chemical digestion, on the other hand, is a complex process that reduces food into its chemical building blocks, which are then absorbed to nourish the cells of the body ([link]). In this section, you will look more closely at the processes of chemical digestion and absorption.

Digestion and Absorption



Digestion begins in the mouth and continues as food travels through the small intestine. Most absorption occurs in the small intestine.

Chemical Digestion

Large food molecules (for example, proteins, lipids, nucleic acids, and starches) must be broken down into subunits that are small enough to be absorbed by the lining of the alimentary canal. This is accomplished by enzymes through hydrolysis. The many enzymes involved in chemical digestion are summarized in [link].

The Digestive Enzymes

The Digestive Enzymes

Enzyme Category	Enzyme Name	Source	Substrate	Product
Salivary Enzymes	Lingual lipase	Lingual glands	Triglycerides	Free fatty acids, and mono- and diglycerides
Salivary Enzymes	Salivary amylase	Salivary glands	Polysaccharides	Disaccharides and trisaccharides
Gastric enzymes	Gastric lipase	Chief cells	Triglycerides	Fatty acids and monoacylglycerides
Gastric enzymes	Pepsin*	Chief cells	Proteins	Peptides
Brush border enzymes	α-Dextrinase	Small intestine	α-Dextrins	Glucose
Brush border enzymes	Enteropeptidase	Small intestine	Trypsinogen	Trypsin
Brush border enzymes	Lactase	Small intestine	Lactose	Glucose and galactose
Brush border enzymes	Maltase	Small intestine	Maltose	Glucose
Brush border enzymes	Nucleosidases and phosphatases	Small intestine	Nucleotides	Phosphates, nitrogenous bases, and pentoses
Brush border enzymes	Peptidases	Small intestine	Aminopeptidase: amino acids at the amino end of peptides Dipeptidase: dipeptides	Aminopeptidase: amino acids and peptides Dipeptidase: amino acids
Brush border enzymes	Sucrase	Small intestine	Sucrose	Glucose and fructose

The Digestive Enzymes

Enzyme Category	Enzyme Name	Source	Substrate	Product
Pancreatic enzymes	Carboxy-peptidase*	Pancreatic acinar cells	Amino acids at the carboxyl end of peptides	Amino acids and peptides
Pancreatic enzymes	Chymotrypsin*	Pancreatic acinar cells	Proteins	Peptides
Pancreatic enzymes	Elastase*	Pancreatic acinar cells	Proteins	Peptides
Pancreatic enzymes	Nucleases	Pancreatic acinar cells	Ribonuclease: ribonucleic acids Deoxyribonuclease: deoxyribonucleic acids	Nucleotides
Pancreatic enzymes	Pancreatic amylase	Pancreatic acinar cells	Polysaccharides (starches)	α-Dextrins, disaccharides (maltose), trisaccharides (maltotriose)
Pancreatic enzymes	Pancreatic lipase	Pancreatic acinar cells	Triglycerides that have been emulsified by bile salts	Fatty acids and monoacylglycerides
Pancreatic enzymes	Trypsin*	Pancreatic acinar cells	Proteins	Peptides

*These enzymes have been activated by other substances.

Carbohydrate Digestion

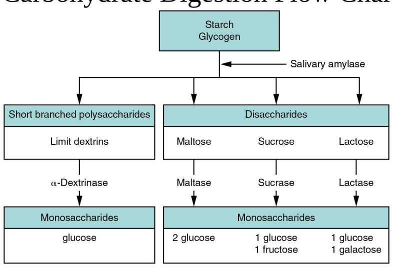
The average American diet is about 50 percent carbohydrates, which may be classified according to the number of monomers they contain of simple sugars (monosaccharides and disaccharides) and/or complex sugars (polysaccharides). Glucose, galactose, and fructose are the three monosaccharides that are commonly consumed and are readily absorbed. Your digestive system is also able to break down the disaccharide sucrose (regular table sugar: glucose + fructose), lactose (milk sugar: glucose + galactose), and maltose (grain sugar: glucose + glucose), and the polysaccharides glycogen and starch (chains of monosaccharides). Your bodies do not produce enzymes that can break down most fibrous polysaccharides, such as cellulose. While indigestible

polysaccharides do not provide any nutritional value, they do provide dietary fiber, which helps propel food through the alimentary canal.

The chemical digestion of starches begins in the mouth and has been reviewed above.

In the small intestine, **pancreatic amylase** does the ‘heavy lifting’ for starch and carbohydrate digestion ([link]). After amylases break down starch into smaller fragments, the brush border enzyme **α-dextrinase** starts working on **α-dextrin**, breaking off one glucose unit at a time. Three brush border enzymes hydrolyze sucrose, lactose, and maltose into monosaccharides. **Sucrase** splits sucrose into one molecule of fructose and one molecule of glucose; **maltase** breaks down maltose and maltotriose into two and three glucose molecules, respectively; and **lactase** breaks down lactose into one molecule of glucose and one molecule of galactose. Insufficient lactase can lead to lactose intolerance.

Carbohydrate Digestion Flow Chart



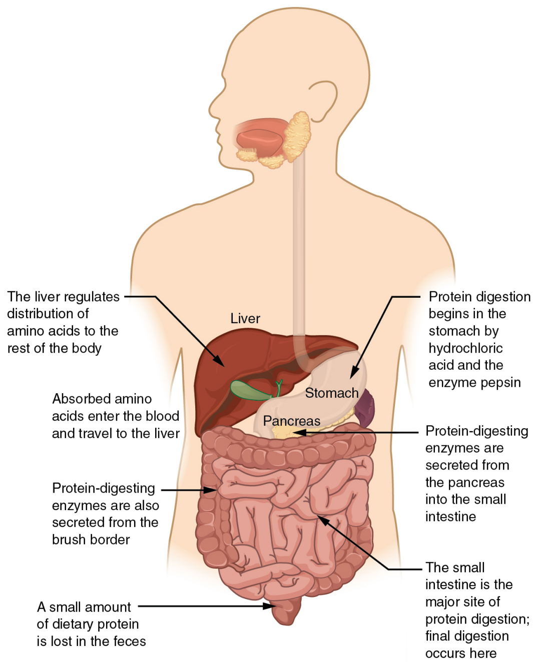
Carbohydrates are broken down into their monomers in a series of steps.

Protein Digestion

Proteins are polymers composed of amino acids linked by peptide bonds to form long chains. Digestion reduces them to their constituent amino acids. You usually consume about 15 to 20 percent of your total calorie intake as protein.

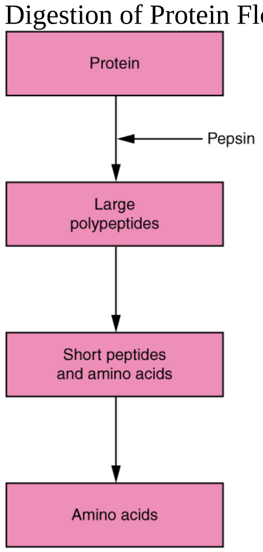
The digestion of protein starts in the stomach, where HCl and pepsin break proteins into smaller polypeptides, which then travel to the small intestine ([link]). Chemical digestion in the small intestine is continued by pancreatic enzymes, including chymotrypsin and trypsin, each of which act on specific bonds in amino acid sequences. At the same time, the cells of the brush border secrete enzymes such as **aminopeptidase** and **dipeptidase**, which further break down peptide chains. This results in molecules small enough to enter the bloodstream ([link]).

Digestion of Protein



The digestion of protein begins in the stomach and is completed in the small intestine.

Digestion of Protein Flow Chart



Proteins are successively broken down into their amino acid components.

Lipid Digestion

A healthy diet limits lipid intake to 35 percent of total calorie intake. The most common dietary lipids are triglycerides, which are made up of a glycerol molecule bound to three fatty acid chains. Small amounts of dietary cholesterol and phospholipids are also consumed.

The three lipases responsible for lipid digestion are lingual lipase, gastric lipase, and **pancreatic lipase**. However, because the pancreas is the only consequential source of lipase, virtually all lipid digestion occurs in the small intestine. Pancreatic lipase breaks down each triglyceride into two free fatty acids and a monoglyceride. The fatty acids include both short-chain (less than 10 to 12 carbons) and long-chain fatty acids.

Nucleic Acid Digestion

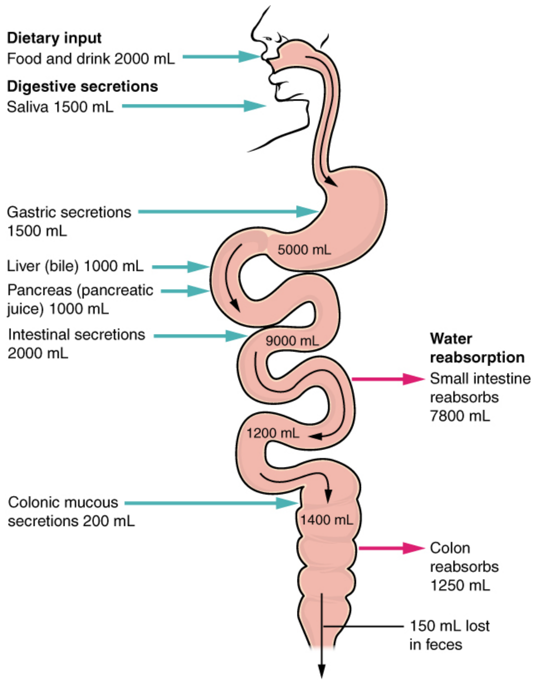
The nucleic acids DNA and RNA are found in most of the foods you eat. Two types of **pancreatic nuclease** are responsible for their digestion: **deoxyribonuclease**, which digests DNA, and **ribonuclease**, which digests RNA. The nucleotides produced by this digestion are further broken down by two intestinal brush border enzymes (**nucleosidase** and **phosphatase**) into pentoses, phosphates, and nitrogenous bases, which can be absorbed through the alimentary canal wall. The large food molecules that must be broken down into subunits are summarized [link]

Absorbable Food Substances	
Source	**Substance**
Carbohydrates	Monosaccharides: glucose, galactose, and fructose
Proteins	Single amino acids, dipeptides, and tripeptides
Triglycerides	Monoacylglycerides, glycerol, and free fatty acids
Nucleic acids	Pentose sugars, phosphates, and nitrogenous bases

Absorption

The mechanical and digestive processes have one goal: to convert food into molecules small enough to be absorbed by the epithelial cells of the intestinal villi. The absorptive capacity of the alimentary canal is almost endless. Each day, the alimentary canal processes up to 10 liters of food, liquids, and GI secretions, yet less than one liter enters the large intestine. Almost all ingested food, 80 percent of electrolytes, and 90 percent of water are absorbed in the small intestine. Although the entire small intestine is involved in the absorption of water and lipids, most absorption of carbohydrates and proteins occurs in the jejunum. Notably, bile salts and vitamin B_{12} are absorbed in the terminal ileum. By the time chyme passes from the ileum into the large intestine, it is essentially indigestible food residue (mainly plant fibers like cellulose), some water, and millions of bacteria ([link]).

Digestive Secretions and Absorption of Water



Absorption is a complex process, in which nutrients from digested food are harvested.

Absorption can occur through five mechanisms: (1) active transport, (2) passive diffusion, (3) facilitated diffusion, (4) co-transport (or secondary active transport), and (5) endocytosis. As you will recall from Chapter 3, active transport refers to the movement of a substance across a cell membrane going from an area of lower concentration to an area of higher concentration (up the concentration gradient). In this type of transport, proteins within the cell membrane act as “pumps,” using cellular energy (ATP) to move the substance. Passive diffusion refers to the movement of substances from an area of higher concentration to an area of lower concentration, while facilitated diffusion refers to the movement of substances from an area of higher to an area of lower concentration using a carrier protein in the cell membrane. Co-transport uses the movement of one molecule through the membrane from higher to lower concentration to power the movement of another from lower to higher. Finally, endocytosis is a transportation process in which the cell membrane engulfs material. It requires energy, generally in the form of ATP.

Because the cell’s plasma membrane is made up of hydrophobic phospholipids, water-soluble nutrients must use transport molecules embedded in the membrane to enter cells. Moreover, substances cannot pass between the epithelial cells of the intestinal mucosa because these cells are bound together by tight junctions. Thus, substances can only enter blood capillaries by passing through the apical surfaces of epithelial cells and into the interstitial fluid. Water-soluble nutrients enter the capillary blood in the villi and travel to the liver via the hepatic portal vein.

In contrast to the water-soluble nutrients, lipid-soluble nutrients can diffuse through the plasma membrane. Once inside the cell, they are packaged for transport via the base of the cell and then enter the lacteals of the villi to be transported by lymphatic vessels to the systemic circulation via the thoracic duct. The absorption of most nutrients through the mucosa of the intestinal villi requires active transport fueled by ATP. The routes of absorption for each food category are summarized in [link].

Absorption in the Alimentary Canal				
Food	**Breakdown products**	**Absorption mechanism**	**Entry to bloodstream**	**Destination**
Carbohydrates	Glucose	Co-transport with sodium ions	Capillary blood in villi	Liver via hepatic portal vein
Carbohydrates	Galactose	Co-transport with sodium ions	Capillary blood in villi	Liver via hepatic portal vein
Carbohydrates	Fructose	Facilitated diffusion	Capillary blood in villi	Liver via hepatic portal vein
Protein	Amino acids	Co-transport with sodium ions	Capillary blood in villi	Liver via hepatic portal vein
Lipids	Long-chain fatty acids	Diffusion into intestinal cells, where they are combined with proteins to create chylomicrons	Lacteals of villi	Systemic circulation via lymph entering thoracic duct
Lipids	Monoacylglycerides	Diffusion into intestinal cells, where they are combined with proteins to create chylomicrons	Lacteals of villi	Systemic circulation via lymph entering thoracic duct
Lipids	Short-chain fatty acids	Simple diffusion	Capillary blood in villi	Liver via hepatic portal vein
Lipids	Glycerol	Simple diffusion	Capillary blood in villi	Liver via hepatic portal vein
Nucleic Acids	Nucleic acid digestion products	Active transport via membrane carriers	Capillary blood in villi	Liver via hepatic portal vein

Carbohydrate Absorption

All carbohydrates are absorbed in the form of monosaccharides. The small intestine is highly efficient at this, absorbing monosaccharides at an estimated rate of 120 grams per hour. All normally digested dietary

carbohydrates are absorbed; indigestible fibers are eliminated in the feces. The monosaccharides glucose and galactose are transported into the epithelial cells by common protein carriers via secondary active transport (that is, co-transport with sodium ions). The monosaccharides leave these cells via facilitated diffusion and enter the capillaries through intercellular clefts. The monosaccharide fructose (which is in fruit) is absorbed and transported by facilitated diffusion alone. The monosaccharides combine with the transport proteins immediately after the disaccharides are broken down.

Protein Absorption

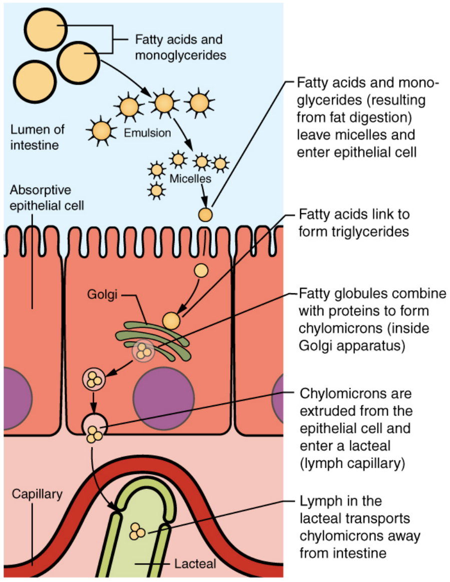
Active transport mechanisms, primarily in the duodenum and jejunum, absorb most proteins as their breakdown products, amino acids. Almost all (95 to 98 percent) protein is digested and absorbed in the small intestine. The type of carrier that transports an amino acid varies. Most carriers are linked to the active transport of sodium. Short chains of two amino acids (dipeptides) or three amino acids (tripeptides) are also transported actively. However, after they enter the absorptive epithelial cells, they are broken down into their amino acids before leaving the cell and entering the capillary blood via diffusion.

Lipid Absorption

About 95 percent of lipids are absorbed in the small intestine. Bile salts not only speed up lipid digestion, they are also essential to the absorption of the end products of lipid digestion. Short-chain fatty acids are relatively water soluble and can enter the absorptive cells (enterocytes) directly. The small size of short-chain fatty acids enables them to be absorbed by enterocytes via simple diffusion, and then take the same path as monosaccharides and amino acids into the blood capillary of a villus.

The large and hydrophobic long-chain fatty acids and monoacylglycerides are not so easily suspended in the watery intestinal chyme. However, bile salts and lecithin resolve this issue by enclosing them in a **micelle**, which is a tiny sphere with polar (hydrophilic) ends facing the watery environment and hydrophobic tails turned to the interior, creating a receptive environment for the long-chain fatty acids. The core also includes cholesterol and fat-soluble vitamins. Without micelles, lipids would sit on the surface of chyme and never come in contact with the absorptive surfaces of the epithelial cells. Micelles can easily squeeze between microvilli and get very near the luminal cell surface. At this point, lipid substances exit the micelle and are absorbed via simple diffusion.

The free fatty acids and monoacylglycerides that enter the epithelial cells are reincorporated into triglycerides. The triglycerides are mixed with phospholipids and cholesterol, and surrounded with a protein coat. This new complex, called a **chylomicron**, is a water-soluble lipoprotein. After being processed by the Golgi apparatus, chylomicrons are released from the cell ([link]). Too big to pass through the basement membranes of blood capillaries, chylomicrons instead enter the large pores of lacteals. The lacteals come together to form the lymphatic vessels. The chylomicrons are transported in the lymphatic vessels and empty through the thoracic duct into the subclavian vein of the circulatory system. Once in the bloodstream, the enzyme **lipoprotein lipase** breaks down the triglycerides of the chylomicrons into free fatty acids and glycerol. These breakdown products then pass through capillary walls to be used for energy by cells or stored in adipose tissue as fat. Liver cells combine the remaining chylomicron remnants with proteins, forming lipoproteins that transport cholesterol in the blood.
Lipid Absorption



Unlike amino acids and simple sugars, lipids are transformed as they are absorbed through epithelial cells.

Nucleic Acid Absorption

The products of nucleic acid digestion—pentose sugars, nitrogenous bases, and phosphate ions—are transported by carriers across the villus epithelium via active transport. These products then enter the bloodstream.

Mineral Absorption

The electrolytes absorbed by the small intestine are from both GI secretions and ingested foods. Since electrolytes dissociate into ions in water, most are absorbed via active transport throughout the entire small intestine. During absorption, co-transport mechanisms result in the accumulation of sodium ions inside the cells, whereas anti-port mechanisms reduce the potassium ion concentration inside the cells. To restore the sodium-potassium gradient across the cell membrane, a sodium-potassium pump requiring ATP pumps sodium out and potassium in.

In general, all minerals that enter the intestine are absorbed, whether you need them or not. Iron and calcium are exceptions; they are absorbed in the duodenum in amounts that meet the body's current requirements, as follows:

Iron—The ionic iron needed for the production of hemoglobin is absorbed into mucosal cells via active transport. Once inside mucosal cells, ionic iron binds to the protein ferritin, creating iron-ferritin complexes that store iron until needed. When the body has enough iron, most of the stored iron is lost when worn-out epithelial cells slough off. When the body needs iron because, for example, it is lost during acute or chronic bleeding, there is increased uptake of iron from the intestine and accelerated release of iron into the

bloodstream. Since women experience significant iron loss during menstruation, they have around four times as many iron transport proteins in their intestinal epithelial cells as do men.

Calcium—Blood levels of ionic calcium determine the absorption of dietary calcium. When blood levels of ionic calcium drop, parathyroid hormone (PTH) secreted by the parathyroid glands stimulates the release of calcium ions from bone matrices and increases the reabsorption of calcium by the kidneys. PTH also upregulates the activation of vitamin D in the kidney, which then facilitates intestinal calcium ion absorption.

Vitamin Absorption

The small intestine absorbs the vitamins that occur naturally in food and supplements. Fat-soluble vitamins (A, D, E, and K) are absorbed along with dietary lipids in micelles via simple diffusion. This is why you are advised to eat some fatty foods when you take fat-soluble vitamin supplements. Most water-soluble vitamins (including most B vitamins and vitamin C) also are absorbed by simple diffusion. An exception is vitamin B_{12}, which is a very large molecule. Intrinsic factor secreted in the stomach binds to vitamin B_{12}, preventing its digestion and creating a complex that binds to mucosal receptors in the terminal ileum, where it is taken up by endocytosis.

Water Absorption

Each day, about nine liters of fluid enter the small intestine. About 2.3 liters are ingested in foods and beverages, and the rest is from GI secretions. About 90 percent of this water is absorbed in the small intestine. Water absorption is driven by the concentration gradient of the water: The concentration of water is higher in chyme than it is in epithelial cells. Thus, water moves down its concentration gradient from the chyme into cells. As noted earlier, much of the remaining water is then absorbed in the colon.

Chapter Review

The small intestine is the site of most chemical digestion and almost all absorption. Chemical digestion breaks large food molecules down into their chemical building blocks, which can then be absorbed through the intestinal wall and into the general circulation. Intestinal brush border enzymes and pancreatic enzymes are responsible for the majority of chemical digestion. The breakdown of fat also requires bile.

Most nutrients are absorbed by transport mechanisms at the apical surface of enterocytes. Exceptions include lipids, fat-soluble vitamins, and most water-soluble vitamins. With the help of bile salts and lecithin, the dietary fats are emulsified to form micelles, which can carry the fat particles to the surface of the enterocytes. There, the micelles release their fats to diffuse across the cell membrane. The fats are then reassembled into triglycerides and mixed with other lipids and proteins into chylomicrons that can pass into lacteals. Other absorbed monomers travel from blood capillaries in the villus to the hepatic portal vein and then to the liver.

Review Questions

Exercise:

Problem: Where does the chemical digestion of starch begin?

a. mouth
b. esophagus
c. stomach
d. small intestine

Solution:

A

Exercise:

Problem: Which of these is involved in the chemical digestion of protein?

a. pancreatic amylase
b. trypsin
c. sucrase
d. pancreatic nuclease

Solution:

B

Exercise:

Problem: Where are most fat-digesting enzymes produced?

a. small intestine
b. gallbladder
c. liver
d. pancreas

Solution:

D

Exercise:

Problem: Which of these nutrients is absorbed mainly in the duodenum?

a. glucose
b. iron
c. sodium
d. water

Solution:

B

Critical Thinking Questions

Exercise:

Problem: Explain the role of bile salts and lecithin in the emulsification of lipids (fats).

Solution:

Bile salts and lecithin can emulsify large lipid globules because they are amphipathic; they have a nonpolar (hydrophobic) region that attaches to the large fat molecules as well as a polar (hydrophilic) region that interacts with the watery chime in the intestine.

Exercise:

Problem: How is vitamin B_{12} absorbed?

Solution:

Intrinsic factor secreted in the stomach binds to the large B_{12} compound, creating a combination that can bind to mucosal receptors in the ileum.

Glossary

α-dextrin
: breakdown product of starch

α-dextrinase
: brush border enzyme that acts on α-dextrins

aminopeptidase
: brush border enzyme that acts on proteins

chylomicron
: large lipid-transport compound made up of triglycerides, phospholipids, cholesterol, and proteins

deoxyribonuclease
: pancreatic enzyme that digests DNA

dipeptidase
: brush border enzyme that acts on proteins

lactase
: brush border enzyme that breaks down lactose into glucose and galactose

lipoprotein lipase
: enzyme that breaks down triglycerides in chylomicrons into fatty acids and monoglycerides

maltase
: brush border enzyme that breaks down maltose and maltotriose into two and three molecules of glucose, respectively

micelle
: tiny lipid-transport compound composed of bile salts and phospholipids with a fatty acid and monoacylglyceride core

nucleosidase
: brush border enzyme that digests nucleotides

pancreatic amylase
: enzyme secreted by the pancreas that completes the chemical digestion of carbohydrates in the small intestine

pancreatic lipase

enzyme secreted by the pancreas that participates in lipid digestion

pancreatic nuclease
: enzyme secreted by the pancreas that participates in nucleic acid digestion

phosphatase
: brush border enzyme that digests nucleotides

ribonuclease
: pancreatic enzyme that digests RNA

sucrase
: brush border enzyme that breaks down sucrose into glucose and fructose

Digestive Systems
By the end of this section, you will be able to:

- Explain the processes of digestion and absorption
- Compare and contrast different types of digestive systems
- Explain the specialized functions of the organs involved in processing food in the body
- Describe the ways in which organs work together to digest food and absorb nutrients

Animals obtain their nutrition from the consumption of other organisms. Depending on their diet, animals can be classified into the following categories: plant eaters (herbivores), meat eaters (carnivores), and those that eat both plants and animals (omnivores). The nutrients and macromolecules present in food are not immediately accessible to the cells. There are a number of processes that modify food within the animal body in order to make the nutrients and organic molecules accessible for cellular function. As animals evolved in complexity of form and function, their digestive systems have also evolved to accommodate their various dietary needs.

Herbivores, Omnivores, and Carnivores

Herbivores are animals whose primary food source is plant-based. Examples of herbivores, as shown in [link] include vertebrates like deer, koalas, and some bird species, as well as invertebrates such as crickets and caterpillars. These animals have evolved digestive systems capable of handling large amounts of plant material. Herbivores can be further classified into frugivores (fruit-eaters), granivores (seed eaters), nectivores (nectar feeders), and folivores (leaf eaters).

Herbivores, like this (a) mule deer and (b) monarch caterpillar, eat primarily plant material. (credit a: modification of work by Bill Ebbesen; credit b: modification of work by Doug Bowman)

Carnivores are animals that eat other animals. The word carnivore is derived from Latin and literally means “meat eater.” Wild cats such as lions, shown in [link]**a** and tigers are examples of vertebrate carnivores, as are snakes and sharks, while invertebrate carnivores include sea stars, spiders, and ladybugs, shown in [link]**b**. Obligate carnivores are those that rely entirely on animal flesh to obtain their nutrients; examples of obligate carnivores are members of the cat family, such as lions and cheetahs. Facultative carnivores are those that also eat non-animal food in addition to animal food. Note that there is no clear line that differentiates facultative carnivores from omnivores; dogs would be considered facultative carnivores.

(a) (b)

Carnivores like the (a) lion eat primarily meat. The (b) ladybug is also a carnivore that consumes small insects called aphids. (credit a: modification of work by Kevin Pluck; credit b: modification of work by Jon Sullivan)

Omnivores are animals that eat both plant- and animal-derived food. In Latin, omnivore means to eat everything. Humans, bears (shown in [link]**a**), and chickens are example of vertebrate omnivores; invertebrate omnivores include cockroaches and crayfish (shown in [link]**b**).

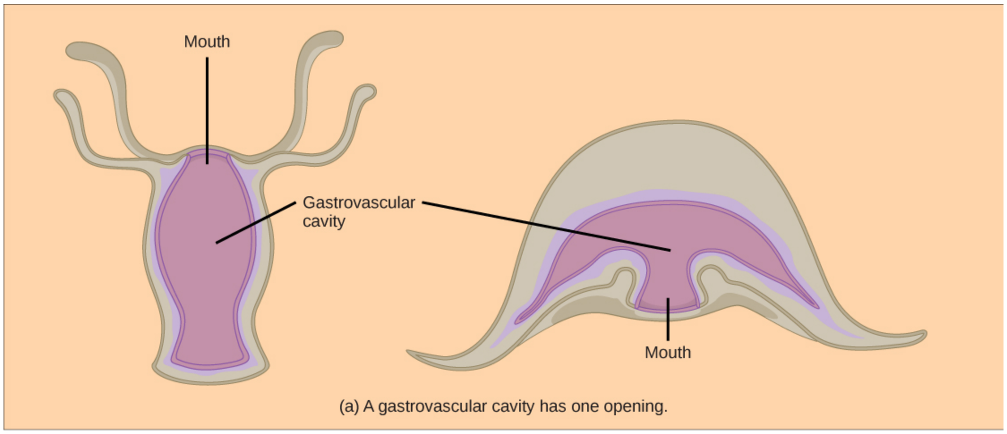
(a) (b)

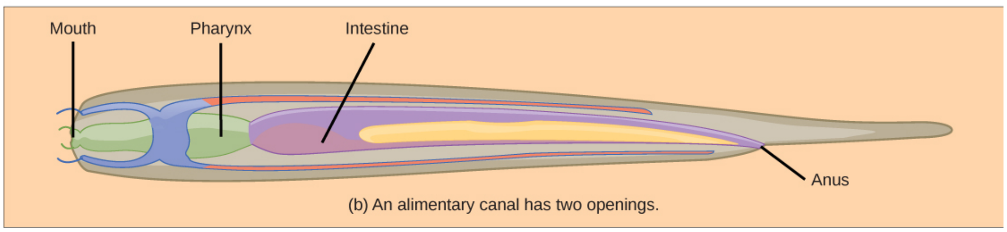
Omnivores like the (a) bear and (b) crayfish eat both plant and animal based food. (credit a: modification of work by Dave Menke; credit b: modification of work by Jon Sullivan)

Invertebrate Digestive Systems

Animals have evolved different types of digestive systems to aid in the digestion of the different foods they consume. The simplest example is that of a **gastrovascular cavity** and is found in organisms with only one opening for digestion. Platyhelminthes (flatworms), Ctenophora (comb jellies), and Cnidaria (coral, jelly fish, and sea anemones) use this type of digestion. Gastrovascular cavities, as shown in [link]**a**, are typically a blind tube or cavity with only one opening, the “mouth”, which also serves as an “anus”. Ingested material enters the mouth and passes through a hollow, tubular cavity. Cells within the cavity secrete digestive enzymes that break down the food. The food particles are engulfed by the cells lining the gastrovascular cavity.

The **alimentary canal**, shown in [link]**b**, is a more advanced system: it consists of one tube with a mouth at one end and an anus at the other. Earthworms are an example of an animal with an alimentary canal. Once the food is ingested through the mouth, it passes through the esophagus and is stored in an organ called the crop; then it passes into the gizzard where it is churned and digested. From the gizzard, the food passes through the intestine, the nutrients are absorbed, and the waste is eliminated as feces, called castings, through the anus.





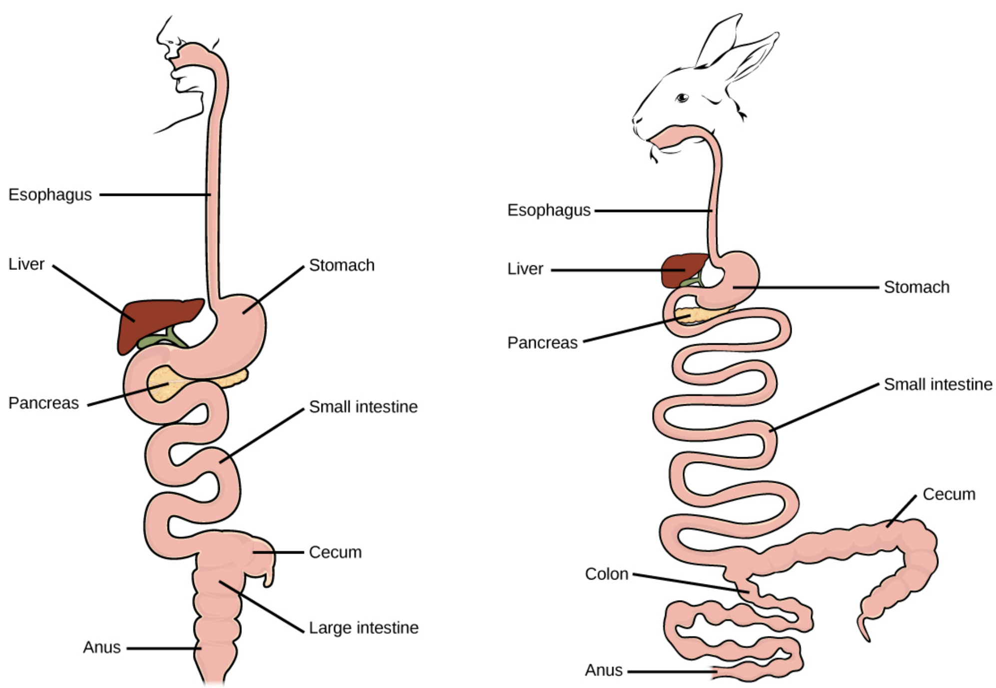
(a) A gastrovascular cavity has a single opening through which food is ingested and waste is excreted, as shown in this hydra and in this jellyfish medusa. (b) An alimentary canal has two openings: a mouth for ingesting food, and an anus for eliminating waste, as shown in this nematode.

Vertebrate Digestive Systems

Vertebrates have evolved more complex digestive systems to adapt to their dietary needs. Some animals have a single stomach, while others have multi-chambered stomachs. Birds have developed a digestive system adapted to eating unmasticated food.

Monogastric: Single-chambered Stomach

As the word **monogastric** suggests, this type of digestive system consists of one (“mono”) stomach chamber (“gastric”). Humans and many animals have a monogastric digestive system as illustrated in [link]**ab**. The process of digestion begins with the mouth and the intake of food. The teeth play an important role in masticating (chewing) or physically breaking down food into smaller particles. The enzymes present in saliva also begin to chemically break down food. The esophagus is a long tube that connects the mouth to the stomach. Using peristalsis, or wave-like smooth muscle contractions, the muscles of the esophagus push the food towards the stomach. In order to speed up the actions of enzymes in the stomach, the stomach is an extremely acidic environment, with a pH between 1.5 and 2.5. The gastric juices, which include enzymes in the stomach, act on the food particles and continue the process of digestion. Further breakdown of food takes place in the small intestine where enzymes produced by the liver, the small intestine, and the pancreas continue the process of digestion. The nutrients are absorbed into the blood stream across the epithelial cells lining the walls of the small intestines. The waste material travels on to the large intestine where water is absorbed and the drier waste material is compacted into feces; it is stored until it is excreted through the rectum.



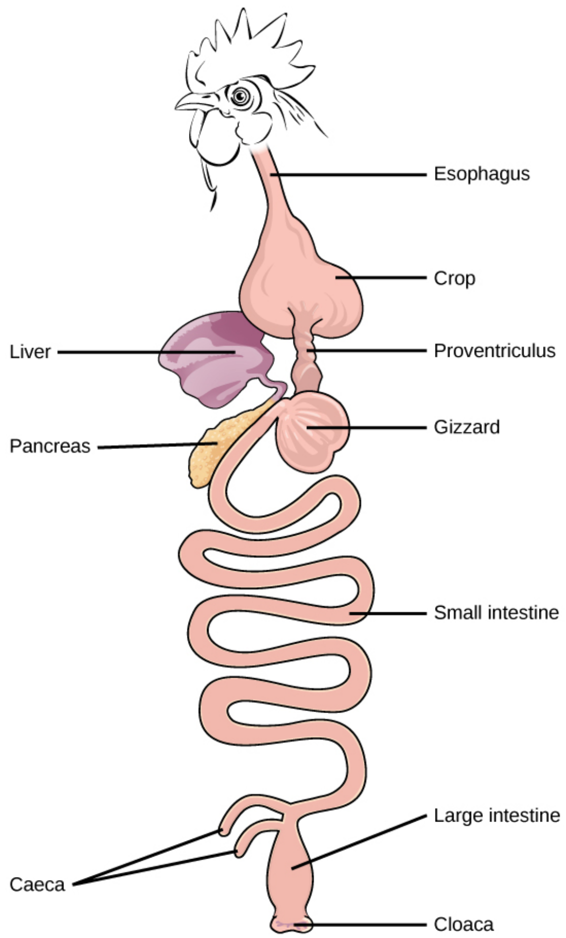
(a) Human digestive system

(b) Rabbit digestive system

(a) Humans and herbivores, such as the (b) rabbit, have a monogastric digestive system. However, in the rabbit the small intestine and cecum are enlarged to allow more time to digest plant material. The enlarged organ provides more surface area for absorption of nutrients. Rabbits digest their food twice: the first time food passes through the digestive system, it collects in the cecum, and then it passes as soft feces called cecotrophes. The rabbit re-ingests these cecotrophes to further digest them.

Avian

Birds face special challenges when it comes to obtaining nutrition from food. They do not have teeth and so their digestive system, shown in [link], must be able to process un-masticated food. Birds have evolved a variety of beak types that reflect the vast variety in their diet, ranging from seeds and insects to fruits and nuts. Because most birds fly, their metabolic rates are high in order to efficiently process food and keep their body weight low. The stomach of birds has two chambers: the **proventriculus**, where gastric juices are produced to digest the food before it enters the stomach, and the **gizzard**, where the food is stored, soaked, and mechanically ground. The undigested material forms food pellets that are sometimes regurgitated. Most of the chemical digestion and absorption happens in the intestine and the waste is excreted through the cloaca.



The avian esophagus has a pouch, called a crop, which stores food. Food passes from the crop to the first of two stomachs, called the proventriculus, which contains digestive juices that break down food. From the proventriculus, the food enters the second stomach, called the gizzard, which grinds food. Some birds swallow stones or grit, which are stored in the gizzard, to aid the grinding process. Birds do not have separate

openings to excrete urine and feces. Instead, uric acid from the kidneys is secreted into the large intestine and combined with waste from the digestive process. This waste is excreted through an opening called the cloaca.

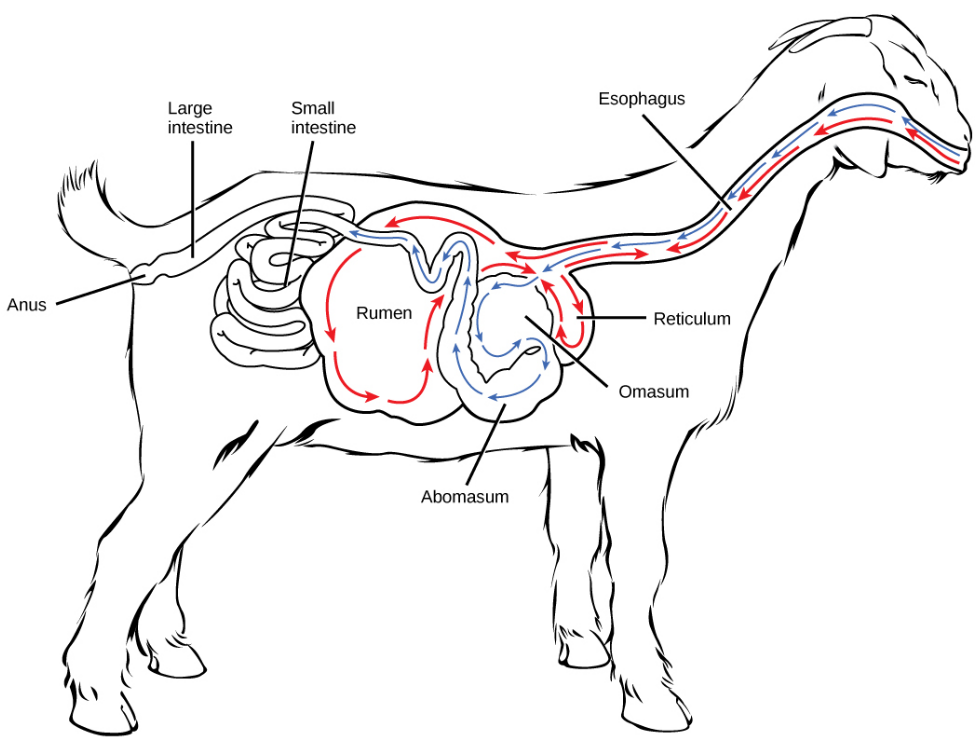
Note:
Evolution Connection
Avian Adaptations
Birds have a highly efficient, simplified digestive system. Recent fossil evidence has shown that the evolutionary divergence of birds from other land animals was characterized by streamlining and simplifying the digestive system. Unlike many other animals, birds do not have teeth to chew their food. In place of lips, they have sharp pointy beaks. The horny beak, lack of jaws, and the smaller tongue of the birds can be traced back to their dinosaur ancestors. The emergence of these changes seems to coincide with the inclusion of seeds in the bird diet. Seed-eating birds have beaks that are shaped for grabbing seeds and the two-compartment stomach allows for delegation of tasks. Since birds need to remain light in order to fly, their metabolic rates are very high, which means they digest their food very quickly and need to eat often. Contrast this with the ruminants, where the digestion of plant matter takes a very long time.

Ruminants

Ruminants are mainly herbivores like cows, sheep, and goats, whose entire diet consists of eating large amounts of **roughage** or fiber. They have evolved digestive systems that help them digest vast amounts of cellulose. An interesting feature of the ruminants’ mouth is that they do not have

upper incisor teeth. They use their lower teeth, tongue and lips to tear and chew their food. From the mouth, the food travels to the esophagus and on to the stomach.

To help digest the large amount of plant material, the stomach of the ruminants is a multi-chambered organ, as illustrated in [link]. The four compartments of the stomach are called the rumen, reticulum, omasum, and abomasum. These chambers contain many microbes that break down cellulose and ferment ingested food. The abomasum is the “true” stomach and is the equivalent of the monogastric stomach chamber where gastric juices are secreted. The four-compartment gastric chamber provides larger space and the microbial support necessary to digest plant material in ruminants. The fermentation process produces large amounts of gas in the stomach chamber, which must be eliminated. As in other animals, the small intestine plays an important role in nutrient absorption, and the large intestine helps in the elimination of waste.



Ruminant animals, such as goats and cows, have four stomachs. The first two stomachs, the rumen and the

reticulum, contain prokaryotes and protists that are able to digest cellulose fiber. The ruminant regurgitates cud from the reticulum, chews it, and swallows it into a third stomach, the omasum, which removes water. The cud then passes onto the fourth stomach, the abomasum, where it is digested by enzymes produced by the ruminant.

Pseudo-ruminants

Some animals, such as camels and alpacas, are pseudo-ruminants. They eat a lot of plant material and roughage. Digesting plant material is not easy because plant cell walls contain the polymeric sugar molecule cellulose. The digestive enzymes of these animals cannot break down cellulose, but microorganisms present in the digestive system can. Therefore, the digestive system must be able to handle large amounts of roughage and break down the cellulose. Pseudo-ruminants have a three-chamber stomach in the digestive system. However, their cecum—a pouched organ at the beginning of the large intestine containing many microorganisms that are necessary for the digestion of plant materials—is large and is the site where the roughage is fermented and digested. These animals do not have a rumen but have an omasum, abomasum, and reticulum.

Parts of the Digestive System

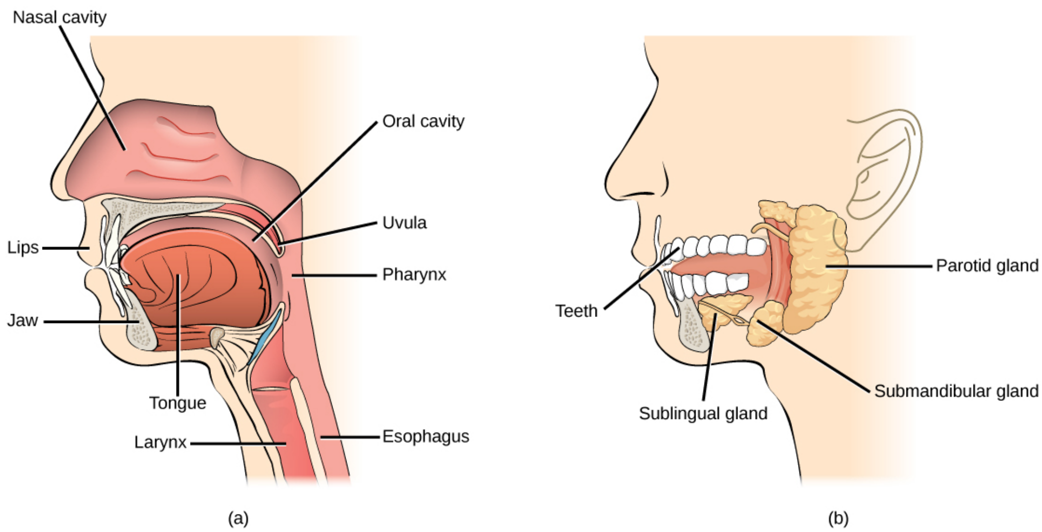
The vertebrate digestive system is designed to facilitate the transformation of food matter into the nutrient components that sustain organisms.

Oral Cavity

The oral cavity, or mouth, is the point of entry of food into the digestive system, illustrated in [link]. The food consumed is broken into smaller

particles by mastication, the chewing action of the teeth. All mammals have teeth and can chew their food.

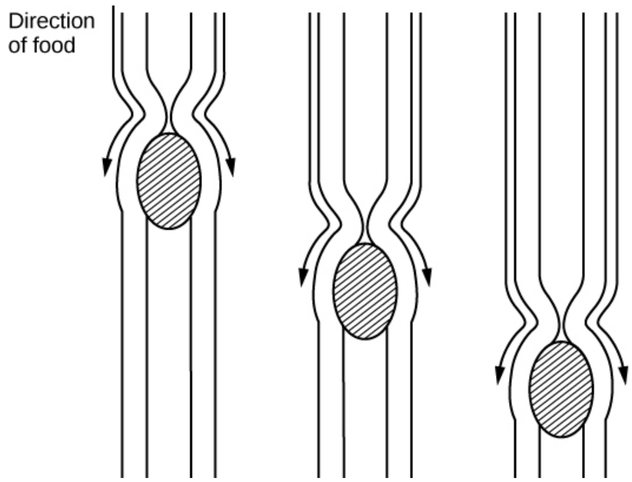
The extensive chemical process of digestion begins in the mouth. As food is being chewed, saliva, produced by the salivary glands, mixes with the food. Saliva is a watery substance produced in the mouths of many animals. There are three major glands that secrete saliva—the parotid, the submandibular, and the sublingual. Saliva contains mucus that moistens food and buffers the pH of the food. Saliva also contains immunoglobulins and lysozymes, which have antibacterial action to reduce tooth decay by inhibiting growth of some bacteria. Saliva also contains an enzyme called **salivary amylase** that begins the process of converting starches in the food into a disaccharide called maltose. Another enzyme called **lipase** is produced by the cells in the tongue. Lipases are a class of enzymes that can break down triglycerides. The lingual lipase begins the breakdown of fat components in the food. The chewing and wetting action provided by the teeth and saliva prepare the food into a mass called the **bolus** for swallowing. The tongue helps in swallowing—moving the bolus from the mouth into the pharynx. The pharynx opens to two passageways: the trachea, which leads to the lungs, and the esophagus, which leads to the stomach. The trachea has an opening called the glottis, which is covered by a cartilaginous flap called the epiglottis. When swallowing, the epiglottis closes the glottis and food passes into the esophagus and not the trachea. This arrangement allows food to be kept out of the trachea.



Digestion of food begins in the (a) oral cavity. Food is masticated by teeth and moistened by saliva secreted from the (b) salivary glands. Enzymes in the saliva begin to digest starches and fats. With the help of the tongue, the resulting bolus is moved into the esophagus by swallowing. (credit: modification of work by the National Cancer Institute)

Esophagus

The **esophagus** is a tubular organ that connects the mouth to the stomach. The chewed and softened food passes through the esophagus after being swallowed. The smooth muscles of the esophagus undergo a series of wave like movements called **peristalsis** that push the food toward the stomach, as illustrated in [link]. The peristalsis wave is unidirectional—it moves food from the mouth to the stomach, and reverse movement is not possible. The peristaltic movement of the esophagus is an involuntary reflex; it takes place in response to the act of swallowing.



The esophagus transfers food from the mouth to the stomach through peristaltic movements.

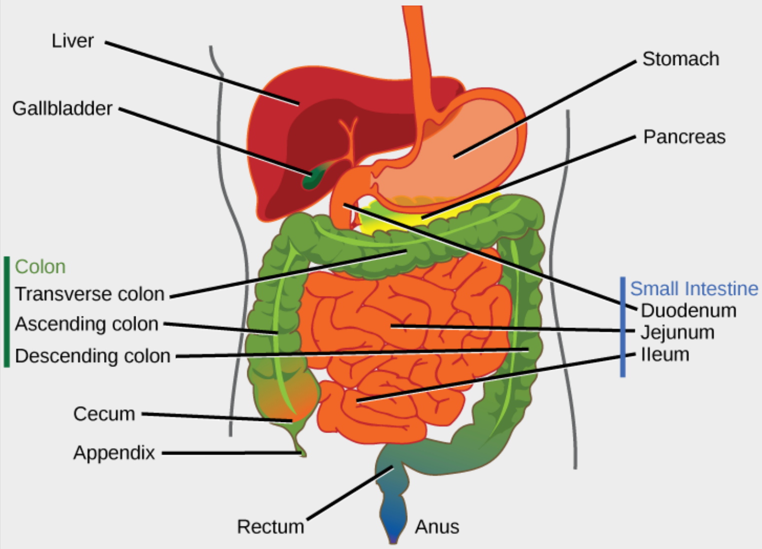
A ring-like muscle called a **sphincter** forms valves in the digestive system. The gastro-esophageal sphincter is located at the stomach end of the esophagus. In response to swallowing and the pressure exerted by the bolus of food, this sphincter opens, and the bolus enters the stomach. When there is no swallowing action, this sphincter is shut and prevents the contents of the stomach from traveling up the esophagus. Many animals have a true sphincter; however, in humans, there is no true sphincter, but the esophagus remains closed when there is no swallowing action. Acid reflux or “heartburn” occurs when the acidic digestive juices escape into the esophagus.

Stomach

A large part of digestion occurs in the stomach, shown in [link]. The **stomach** is a saclike organ that secretes gastric digestive juices. The pH in the stomach is between 1.5 and 2.5. This highly acidic environment is required for the chemical breakdown of food and the extraction of nutrients. When empty, the stomach is a rather small organ; however, it can expand to

up to 20 times its resting size when filled with food. This characteristic is particularly useful for animals that need to eat when food is available.

Note:
Art Connection



The human stomach has an extremely acidic environment where most of the protein gets digested. (credit: modification of work by Mariana Ruiz Villareal)

Which of the following statements about the digestive system is false?

a. Chyme is a mixture of food and digestive juices that is produced in the stomach.
b. Food enters the large intestine before the small intestine.
c. In the small intestine, chyme mixes with bile, which emulsifies fats.
d. The stomach is separated from the small intestine by the pyloric sphincter.

The stomach is also the major site for protein digestion in animals other than ruminants. Protein digestion is mediated by an enzyme called pepsin in the stomach chamber. **Pepsin** is secreted by the chief cells in the stomach in an inactive form called **pepsinogen**. Pepsin breaks peptide bonds and cleaves proteins into smaller polypeptides; it also helps activate more pepsinogen, starting a positive feedback mechanism that generates more pepsin. Another cell type—parietal cells—secrete hydrogen and chloride ions, which combine in the lumen to form hydrochloric acid, the primary acidic component of the stomach juices. Hydrochloric acid helps to convert the inactive pepsinogen to pepsin. The highly acidic environment also kills many microorganisms in the food and, combined with the action of the enzyme pepsin, results in the hydrolysis of protein in the food. Chemical digestion is facilitated by the churning action of the stomach. Contraction and relaxation of smooth muscles mixes the stomach contents about every 20 minutes. The partially digested food and gastric juice mixture is called **chyme**. Chyme passes from the stomach to the small intestine. Further protein digestion takes place in the small intestine. Gastric emptying occurs within two to six hours after a meal. Only a small amount of chyme is released into the small intestine at a time. The movement of chyme from the stomach into the small intestine is regulated by the pyloric sphincter.

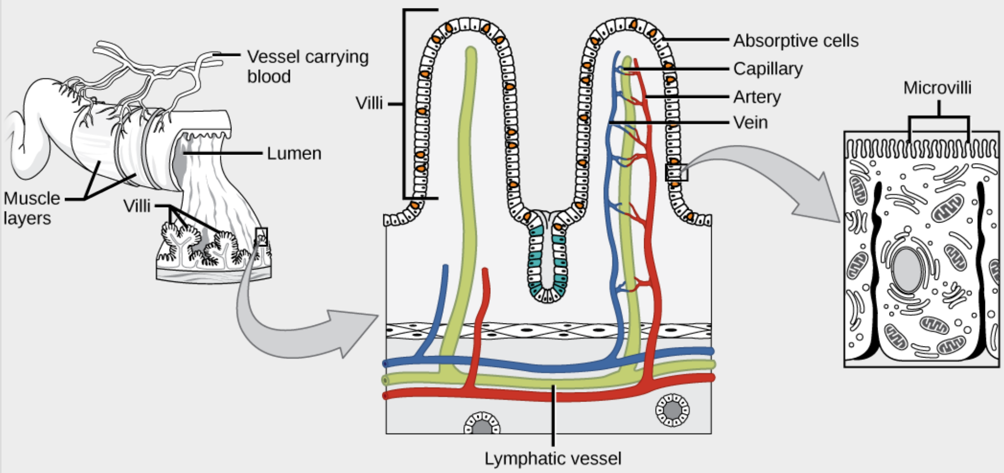
When digesting protein and some fats, the stomach lining must be protected from getting digested by pepsin. There are two points to consider when describing how the stomach lining is protected. First, as previously mentioned, the enzyme pepsin is synthesized in the inactive form. This protects the chief cells, because pepsinogen does not have the same enzyme functionality of pepsin. Second, the stomach has a thick mucus lining that protects the underlying tissue from the action of the digestive juices. When this mucus lining is ruptured, ulcers can form in the stomach. Ulcers are open wounds in or on an organ caused by bacteria (*Helicobacter pylori*) when the mucus lining is ruptured and fails to reform.

Small Intestine

Chyme moves from the stomach to the small intestine. The **small intestine** is the organ where the digestion of protein, fats, and carbohydrates is

completed. The small intestine is a long tube-like organ with a highly folded surface containing finger-like projections called the **villi**. The apical surface of each villus has many microscopic projections called microvilli. These structures, illustrated in [link], are lined with epithelial cells on the luminal side and allow for the nutrients to be absorbed from the digested food and absorbed into the blood stream on the other side. The villi and microvilli, with their many folds, increase the surface area of the intestine and increase absorption efficiency of the nutrients. Absorbed nutrients in the blood are carried into the hepatic portal vein, which leads to the liver. There, the liver regulates the distribution of nutrients to the rest of the body and removes toxic substances, including drugs, alcohol, and some pathogens.

Note:
Art Connection



Villi are folds on the small intestine lining that increase the surface area to facilitate the absorption of nutrients.

Which of the following statements about the small intestine is false?

a. Absorptive cells that line the small intestine have microvilli, small projections that increase surface area and aid in the absorption of food.

b. The inside of the small intestine has many folds, called villi.
c. Microvilli are lined with blood vessels as well as lymphatic vessels.
d. The inside of the small intestine is called the lumen.

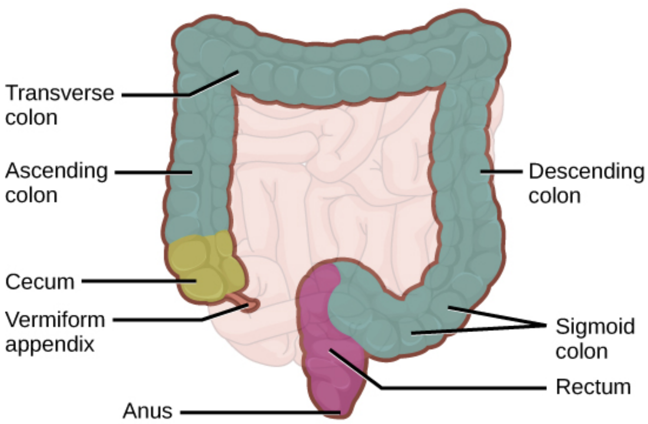
The human small intestine is over 6m long and is divided into three parts: the duodenum, the jejunum, and the ileum. The “C-shaped,” fixed part of the small intestine is called the **duodenum** and is shown in [link]. The duodenum is separated from the stomach by the pyloric sphincter which opens to allow chyme to move from the stomach to the duodenum. In the duodenum, chyme is mixed with pancreatic juices in an alkaline solution rich in bicarbonate that neutralizes the acidity of chyme and acts as a buffer. Pancreatic juices also contain several digestive enzymes. Digestive juices from the pancreas, liver, and gallbladder, as well as from gland cells of the intestinal wall itself, enter the duodenum. **Bile** is produced in the liver and stored and concentrated in the gallbladder. Bile contains bile salts which emulsify lipids while the pancreas produces enzymes that catabolize starches, disaccharides, proteins, and fats. These digestive juices break down the food particles in the chyme into glucose, triglycerides, and amino acids. Some chemical digestion of food takes place in the duodenum. Absorption of fatty acids also takes place in the duodenum.

The second part of the small intestine is called the **jejunum**, shown in [link]. Here, hydrolysis of nutrients is continued while most of the carbohydrates and amino acids are absorbed through the intestinal lining. The bulk of chemical digestion and nutrient absorption occurs in the jejunum.

The **ileum**, also illustrated in [link] is the last part of the small intestine and here the bile salts and vitamins are absorbed into blood stream. The undigested food is sent to the colon from the ileum via peristaltic movements of the muscle. The ileum ends and the large intestine begins at the ileocecal valve. The vermiform, “worm-like,” appendix is located at the ileocecal valve. The appendix of humans secretes no enzymes and has an insignificant role in immunity.

Large Intestine

The **large intestine**, illustrated in [link], reabsorbs the water from the undigested food material and processes the waste material. The human large intestine is much smaller in length compared to the small intestine but larger in diameter. It has three parts: the cecum, the colon, and the rectum. The cecum joins the ileum to the colon and is the receiving pouch for the waste matter. The colon is home to many bacteria or “intestinal flora” that aid in the digestive processes. The colon can be divided into four regions, the ascending colon, the transverse colon, the descending colon and the sigmoid colon. The main functions of the colon are to extract the water and mineral salts from undigested food, and to store waste material. Carnivorous mammals have a shorter large intestine compared to herbivorous mammals due to their diet.



The large intestine reabsorbs water from undigested food and stores waste material until it is eliminated.

Rectum and Anus

The **rectum** is the terminal end of the large intestine, as shown in [link]. The primary role of the rectum is to store the feces until defecation. The feces are propelled using peristaltic movements during elimination. The **anus** is an opening at the far-end of the digestive tract and is the exit point for the waste material. Two sphincters between the rectum and anus control elimination: the inner sphincter is involuntary and the outer sphincter is voluntary.

Accessory Organs

The organs discussed above are the organs of the digestive tract through which food passes. Accessory organs are organs that add secretions (enzymes) that catabolize food into nutrients. Accessory organs include salivary glands, the liver, the pancreas, and the gallbladder. The liver, pancreas, and gallbladder are regulated by hormones in response to the food consumed.

The **liver** is the largest internal organ in humans and it plays a very important role in digestion of fats and detoxifying blood. The liver produces bile, a digestive juice that is required for the breakdown of fatty components of the food in the duodenum. The liver also processes the vitamins and fats and synthesizes many plasma proteins.

The **pancreas** is another important gland that secretes digestive juices. The chyme produced from the stomach is highly acidic in nature; the pancreatic juices contain high levels of bicarbonate, an alkali that neutralizes the acidic chyme. Additionally, the pancreatic juices contain a large variety of enzymes that are required for the digestion of protein and carbohydrates.

The **gallbladder** is a small organ that aids the liver by storing bile and concentrating bile salts. When chyme containing fatty acids enters the duodenum, the bile is secreted from the gallbladder into the duodenum.

Section Summary

Different animals have evolved different types of digestive systems specialized to meet their dietary needs. Humans and many other animals have monogastric digestive systems with a single-chambered stomach. Birds have evolved a digestive system that includes a gizzard where the food is crushed into smaller pieces. This compensates for their inability to masticate. Ruminants that consume large amounts of plant material have a multi-chambered stomach that digests roughage. Pseudo-ruminants have similar digestive processes as ruminants but do not have the four-compartment stomach. Processing food involves ingestion (eating), digestion (mechanical and enzymatic breakdown of large molecules), absorption (cellular uptake of nutrients), and elimination (removal of undigested waste as feces).

Many organs work together to digest food and absorb nutrients. The mouth is the point of ingestion and the location where both mechanical and chemical breakdown of food begins. Saliva contains an enzyme called amylase that breaks down carbohydrates. The food bolus travels through the esophagus by peristaltic movements to the stomach. The stomach has an extremely acidic environment. An enzyme called pepsin digests protein in the stomach. Further digestion and absorption take place in the small intestine. The large intestine reabsorbs water from the undigested food and stores waste until elimination.

Art Connections

Exercise:

Problem:

[link] Which of the following statements about the digestive system is false?

a. Chyme is a mixture of food and digestive juices that is produced in the stomach.
b. Food enters the large intestine before the small intestine.
c. In the small intestine, chyme mixes with bile, which emulsifies fats.

d. The stomach is separated from the small intestine by the pyloric sphincter.

Solution:

[link] B

Exercise:

Problem:

[link] Which of the following statements about the small intestine is false?

a. Absorptive cells that line the small intestine have microvilli, small projections that increase surface area and aid in the absorption of food.
b. The inside of the small intestine has many folds, called villi.
c. Microvilli are lined with blood vessels as well as lymphatic vessels.
d. The inside of the small intestine is called the lumen.

Solution:

[link] C

Review Questions

Exercise:

Problem: Which of the following is a pseudo-ruminant?

a. cow
b. pig
c. crow
d. horse

Solution:

D

Exercise:

Problem: Which of the following statements is untrue?

a. Roughage takes a long time to digest.
b. Birds eat large quantities at one time so that they can fly long distances.
c. Cows do not have upper teeth.
d. In pseudo-ruminants, roughage is digested in the cecum.

Solution:

B

Exercise:

Problem: The acidic nature of chyme is neutralized by _________.

a. potassium hydroxide
b. sodium hydroxide
c. bicarbonates
d. vinegar

Solution:

C

Exercise:

Problem:

The digestive juices from the liver are delivered to the _________.

a. stomach
b. liver
c. duodenum
d. colon

Solution:

C

Free Response

Exercise:

Problem:

How does the polygastric digestive system aid in digesting roughage?

Solution:

Animals with a polygastric digestive system have a multi-chambered stomach. The four compartments of the stomach are called the rumen, reticulum, omasum, and abomasum. These chambers contain many microbes that break down the cellulose and ferment the ingested food. The abomasum is the “true” stomach and is the equivalent of a monogastric stomach chamber where gastric juices are secreted. The four-compartment gastric chamber provides larger space and the microbial support necessary for ruminants to digest plant material.

Exercise:

Problem: How do birds digest their food in the absence of teeth?

Solution:

Birds have a stomach chamber called a gizzard. Here, the food is stored, soaked, and ground into finer particles, often using pebbles.

Once this process is complete, the digestive juices take over in the proventriculus and continue the digestive process.

Exercise:

Problem: What is the role of the accessory organs in digestion?

Solution:

Accessory organs play an important role in producing and delivering digestive juices to the intestine during digestion and absorption. Specifically, the salivary glands, liver, pancreas, and gallbladder play important roles. Malfunction of any of these organs can lead to disease states.

Exercise:

Problem: Explain how the villi and microvilli aid in absorption.

Solution:

The villi and microvilli are folds on the surface of the small intestine. These folds increase the surface area of the intestine and provide more area for the absorption of nutrients.

Glossary

alimentary canal
: tubular digestive system with a mouth and anus

anus
: exit point for waste material

bile
: digestive juice produced by the liver; important for digestion of lipids

bolus

mass of food resulting from chewing action and wetting by saliva

carnivore
animal that consumes animal flesh

chyme
mixture of partially digested food and stomach juices

duodenum
first part of the small intestine where a large part of digestion of carbohydrates and fats occurs

esophagus
tubular organ that connects the mouth to the stomach

gallbladder
organ that stores and concentrates bile

gastrovascular cavity
digestive system consisting of a single opening

gizzard
muscular organ that grinds food

herbivore
animal that consumes strictly plant diet

ileum
last part of the small intestine; connects the small intestine to the large intestine; important for absorption of B-12

jejunum
second part of the small intestine

large intestine
digestive system organ that reabsorbs water from undigested material and processes waste matter

lipase

enzyme that chemically breaks down lipids

liver
: organ that produces bile for digestion and processes vitamins and lipids

monogastric
: digestive system that consists of a single-chambered stomach

omnivore
: animal that consumes both plants and animals

pancreas
: gland that secretes digestive juices

pepsin
: enzyme found in the stomach whose main role is protein digestion

pepsinogen
: inactive form of pepsin

peristalsis
: wave-like movements of muscle tissue

proventriculus
: glandular part of a bird’s stomach

rectum
: area of the body where feces is stored until elimination

roughage
: component of food that is low in energy and high in fiber

ruminant
: animal with a stomach divided into four compartments

salivary amylase
: enzyme found in saliva, which converts carbohydrates to maltose

small intestine
: organ where digestion of protein, fats, and carbohydrates is completed

sphincter
: band of muscle that controls movement of materials throughout the digestive tract

stomach
: saclike organ containing acidic digestive juices

villi
: folds on the inner surface of the small intestine whose role is to increase absorption area

Physical Characteristics of Urine

By the end of this section, you will be able to:

- Compare and contrast blood plasma, glomerular filtrate, and urine characteristics
- Describe the characteristics of a normal urine sample, including normal range of pH, osmolarity, and volume

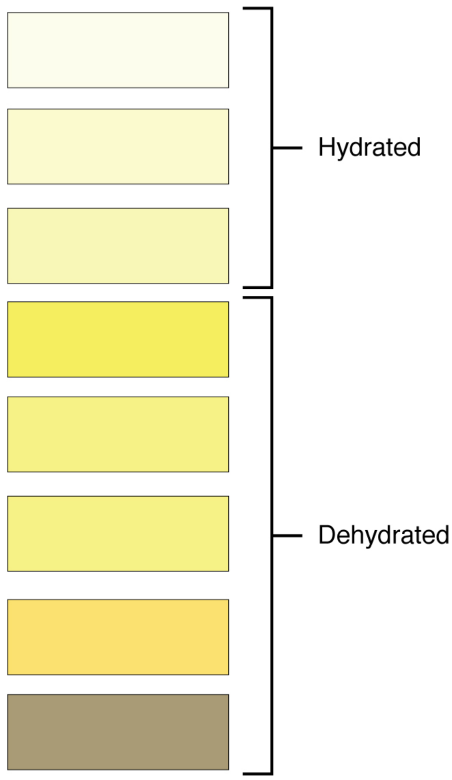
The urinary system's ability to filter the blood resides in about 2 to 3 million tufts of specialized capillaries—the glomeruli—distributed more or less equally between the two kidneys. Because the glomeruli filter the blood based mostly on particle size, large elements like blood cells, platelets, antibodies, and albumen are excluded. The glomerulus is the first part of the nephron, which then continues as a highly specialized tubular structure responsible for creating the final urine composition. All other solutes, such as ions, amino acids, vitamins, and wastes, are filtered to create a filtrate composition very similar to plasma. The glomeruli create about 200 liters (189 quarts) of this filtrate every day, yet you excrete less than two liters of waste you call urine.

Characteristics of the urine change, depending on influences such as water intake, exercise, environmental temperature, nutrient intake, and other factors ([link]). Some of the characteristics such as color and odor are rough descriptors of your state of hydration. For example, if you exercise or work outside, and sweat a great deal, your urine will turn darker and produce a slight odor, even if you drink plenty of water. Athletes are often advised to consume water until their urine is clear. This is good advice; however, it takes time for the kidneys to process body fluids and store it in the bladder. Another way of looking at this is that the quality of the urine produced is an average over the time it takes to make that urine. Producing clear urine may take only a few minutes if you are drinking a lot of water or several hours if you are working outside and not drinking much.

Normal Urine Characteristics	
Characteristic	**Normal values**
Color	Pale yellow to deep amber
Odor	Odorless
Volume	750–2000 mL/24 hour
pH	4.5–8.0
Specific gravity	1.003–1.032
Osmolarity	40–1350 mOsmol/kg
Urobilinogen	0.2–1.0 mg/100 mL
White blood cells	0–2 HPF (per high-power field of microscope)
Leukocyte esterase	None
Protein	None or trace
Bilirubin	<0.3 mg/100 mL
Ketones	None
Nitrites	None
Blood	None
Glucose	None

Urinalysis (urine analysis) often provides clues to renal disease. Normally, only traces of protein are found in urine, and when higher amounts are found, damage to the glomeruli is the likely basis. Unusually large quantities of urine may point to diseases like diabetes mellitus or hypothalamic tumors that cause diabetes insipidus. The color of urine is determined mostly by the breakdown products of red blood cell destruction ([link]). The "heme" of hemoglobin is converted by the liver into water-soluble forms that can be excreted into the bile and indirectly into the urine. This yellow pigment is **urochrome**. Urine color may also be affected by certain foods like beets, berries, and fava beans. A kidney stone or a cancer of the urinary system may produce sufficient bleeding to manifest as pink or even bright red urine. Diseases of the liver or obstructions of bile drainage from the liver impart a dark "tea" or "cola" hue to the urine. Dehydration produces darker, concentrated urine that may also possess the slight odor of ammonia. Most of the ammonia produced from protein breakdown is converted into urea by the liver, so ammonia is rarely detected in fresh urine. The strong ammonia odor you may detect in bathrooms or alleys is due to the breakdown of urea into ammonia by bacteria in the environment. About one in five people detect a distinctive odor in their urine after consuming asparagus; other foods such as onions, garlic, and fish can impart their own aromas! These food-caused odors are harmless.

Urine Color



Urine volume varies considerably. The normal range is one to two liters per day ([link]). The kidneys must produce a minimum urine volume of about 500 mL/day to rid the body of wastes. Output below this level may be caused by severe dehydration or renal disease and is termed **oliguria**. The virtual absence of urine production is termed **anuria**. Excessive urine production is **polyuria**, which may be due to diabetes mellitus or diabetes insipidus. In diabetes mellitus, blood glucose levels exceed the number of available sodium-glucose transporters in the kidney, and glucose appears in the urine. The osmotic nature of glucose attracts water, leading to its loss in the urine. In the case of diabetes insipidus, insufficient pituitary antidiuretic hormone (ADH) release or insufficient numbers of ADH receptors in the collecting ducts means that too few water channels are inserted into the cell membranes that line the collecting ducts of the kidney. Insufficient numbers of water channels (aquaporins) reduce water absorption, resulting in high volumes of very dilute urine.

Urine Volumes		
Volume condition	**Volume**	**Causes**
Normal	1–2 L/day	
Polyuria	>2.5 L/day	Diabetes mellitus; diabetes insipidus; excess caffeine or alcohol; kidney disease; certain drugs, such as diuretics; sickle cell anemia; excessive water intake
Oliguria	300–500 mL/day	Dehydration; blood loss; diarrhea; cardiogenic shock; kidney disease; enlarged prostate
Anuria	<50 mL/day	Kidney failure; obstruction, such as kidney stone or tumor; enlarged prostate

The pH (hydrogen ion concentration) of the urine can vary more than 1000-fold, from a normal low of 4.5 to a maximum of 8.0. Diet can influence pH; meats lower the pH, whereas citrus fruits, vegetables, and dairy products raise the pH. Chronically high or low pH can lead to disorders, such as the development of kidney stones or osteomalacia.

Specific gravity is a measure of the quantity of solutes per unit volume of a solution and is traditionally easier to measure than osmolarity. Urine will always have a specific gravity greater than pure water (water = 1.0) due to the presence of solutes. Laboratories can now measure urine osmolarity directly, which is a more accurate indicator of urinary solutes than **specific gravity**. Remember that osmolarity is the number of osmoles or milliosmoles per liter of fluid (mOsmol/L). Urine osmolarity ranges from a low of 50–100 mOsmol/L to as high as 1200 mOsmol/L H_2O.

Cells are not normally found in the urine. The presence of leukocytes may indicate a urinary tract infection. **Leukocyte esterase** is released by leukocytes; if detected in the urine, it can be taken as indirect evidence of a urinary tract infection (UTI).

Protein does not normally leave the glomerular capillaries, so only trace amounts of protein should be found in the urine, approximately 10 mg/100 mL in a random sample. If excessive protein is detected in the urine, it usually means that the glomerulus is damaged and is allowing protein to "leak" into the filtrate.

Ketones are byproducts of fat metabolism. Finding ketones in the urine suggests that the body is using fat as an energy source in preference to glucose. In diabetes mellitus when there is not enough insulin (type I diabetes mellitus) or because of insulin resistance (type II diabetes mellitus), there is plenty of glucose, but without the action of insulin, the cells cannot take it up, so it remains in the bloodstream. Instead, the cells are forced to use fat as their energy source, and fat consumed at such a level produces excessive ketones as byproducts. These excess ketones will appear in the urine. Ketones may also appear if there is a severe deficiency of proteins or carbohydrates in the diet.

Nitrates (NO_3^-) occur normally in the urine. Gram-negative bacteria metabolize nitrate into nitrite (NO_2^-), and its presence in the urine is indirect evidence of infection.

There should be no blood found in the urine. It may sometimes appear in urine samples as a result of menstrual contamination, but this is not an abnormal condition. Now that you understand what the normal characteristics of urine are, the next section will introduce you to how you store and dispose of this waste product and how you make it.

Chapter Review

The kidney glomerulus filters blood mainly based on particle size to produce a filtrate lacking cells or large proteins. Most of the ions and molecules in the filtrate are needed by the body and must be reabsorbed

farther down the nephron tubules, resulting in the formation of urine. Urine characteristics change depending on water intake, exercise, environmental temperature, and nutrient intake. Urinalysis analyzes characteristics of the urine and is used to diagnose diseases. A minimum of 400 to 500 mL urine must be produced daily to rid the body of wastes. Excessive quantities of urine may indicate diabetes insipidus or diabetes mellitus. The pH range of urine is 4.5 to 8.0, and is affected by diet. Osmolarity ranges from 50 to 1200 milliosmoles, and is a reflection of the amount of water being recovered or lost by renal nephrons.

Review Questions

Exercise:

Problem:

Diabetes insipidus or diabetes mellitus would most likely be indicated by _________.

a. anuria
b. polyuria
c. oliguria
d. none of the above

Solution:

B

Exercise:

Problem: The color of urine is determined mainly by _________.

a. diet
b. filtration rate
c. byproducts of red blood cell breakdown
d. filtration efficiency

Solution:

C

Exercise:

Problem:

Production of less than 50 mL/day of urine is called ________.

a. normal
b. polyuria
c. oliguria
d. anuria

Solution:

D

Critical Thinking Questions

Exercise:

Problem:

What is suggested by the presence of white blood cells found in the urine?

Solution:

The presence of white blood cells found in the urine suggests urinary tract infection.

Exercise:

Problem:

Both diabetes mellitus and diabetes insipidus produce large urine volumes, but how would other characteristics of the urine differ between the two diseases?

Solution:

Diabetes mellitus would result in urine containing glucose, and diabetes insipidus would produce urine with very low osmolarity (low specific gravity, dilute).

Glossary

anuria
: absence of urine produced; production of 50 mL or less per day

leukocyte esterase
: enzyme produced by leukocytes that can be detected in the urine and that serves as an indirect indicator of urinary tract infection

oliguria
: below normal urine production of 400–500 mL/day

polyuria
: urine production in excess of 2.5 L/day; may be caused by diabetes insipidus, diabetes mellitus, or excessive use of diuretics

specific gravity
: weight of a liquid compared to pure water, which has a specific gravity of 1.0; any solute added to water will increase its specific gravity

urinalysis
: analysis of urine to diagnose disease

urochrome
: heme-derived pigment that imparts the typical yellow color of urine

Gross Anatomy of Urine Transport
By the end of this section, you will be able to:

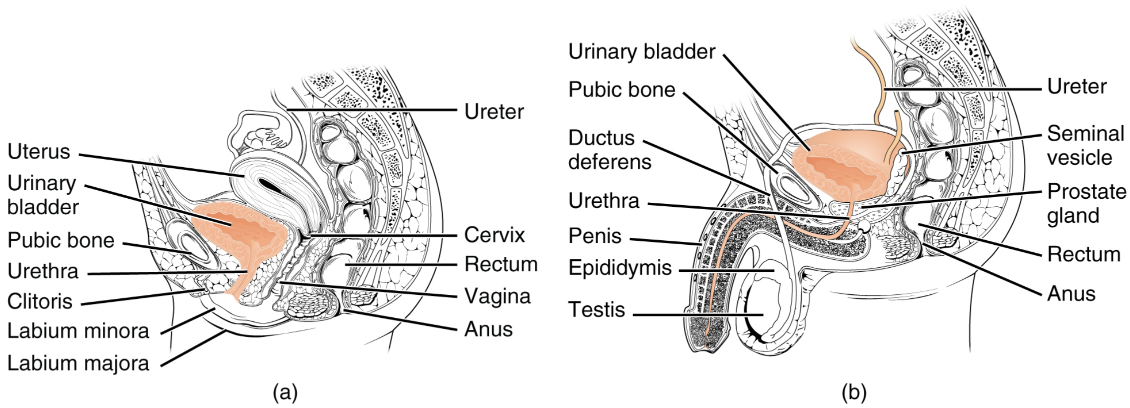
- Identify the ureters, urinary bladder, and urethra, as well as their location, structure, histology, and function
- Compare and contrast male and female urethras
- Describe the micturition reflex
- Describe voluntary and involuntary neural control of micturition

Rather than start with urine formation, this section will start with urine excretion. Urine is a fluid of variable composition that requires specialized structures to remove it from the body safely and efficiently. Blood is filtered, and the filtrate is transformed into urine at a relatively constant rate throughout the day. This processed liquid is stored until a convenient time for excretion. All structures involved in the transport and storage of the urine are large enough to be visible to the naked eye. This transport and storage system not only stores the waste, but it protects the tissues from damage due to the wide range of pH and osmolarity of the urine, prevents infection by foreign organisms, and for the male, provides reproductive functions.

Urethra

The **urethra** transports urine from the bladder to the outside of the body for disposal. The urethra is the only urologic organ that shows any significant anatomic difference between males and females; all other urine transport structures are identical ([link]).
Female and Male Urethras

The urethra transports urine from the bladder to the outside of the body. This image shows (a) a female urethra and (b) a male urethra.



The urethra in both males and females begins inferior and central to the two ureteral openings forming the three points of a triangular-shaped area at the base of the bladder called the **trigone** (Greek tri- = "triangle" and the root of the word "trigonometry"). The urethra tracks posterior and inferior to the pubic symphysis (see [link]**a**). In both males and females, the proximal urethra is lined by transitional epithelium, whereas the terminal portion is a nonkeratinized, stratified squamous epithelium. In the male, pseudostratified columnar epithelium lines the urethra between these two cell types. Voiding is regulated by an involuntary autonomic nervous system-controlled **internal urinary sphincter**, consisting of smooth muscle and voluntary skeletal muscle that forms the **external urinary sphincter** below it.

Female Urethra

The external urethral orifice is embedded in the anterior vaginal wall inferior to the clitoris, superior to the vaginal opening (introitus), and medial to the labia minora. Its short length, about 4 cm, is less of a barrier to fecal bacteria than the longer male urethra and the best explanation for the greater incidence of UTI in women. Voluntary control of the external urethral sphincter is a function of the pudendal nerve. It arises in the sacral region of the spinal cord, traveling via the S2–S4 nerves of the sacral plexus.

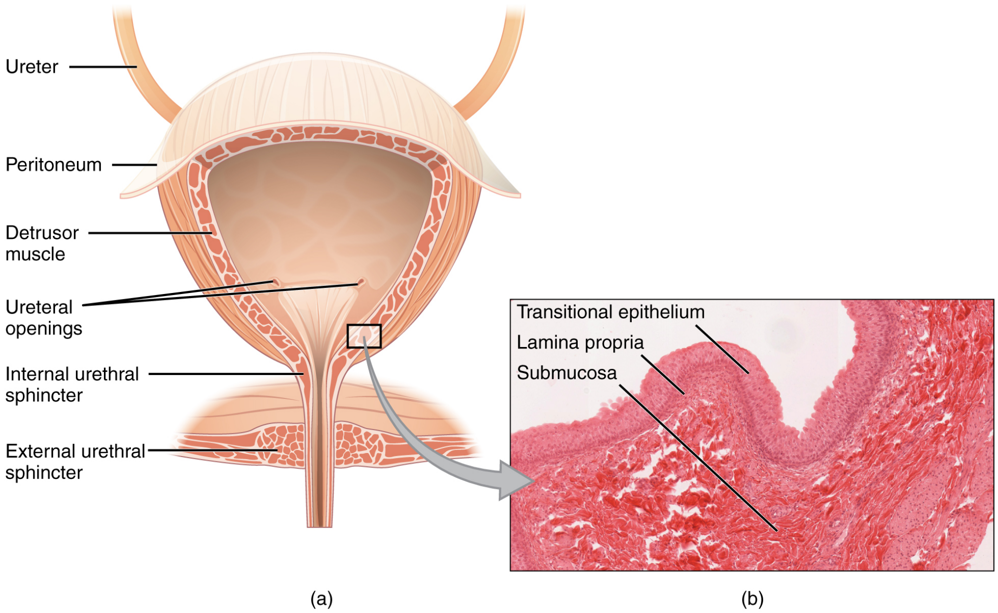
Male Urethra

The male urethra passes through the prostate gland immediately inferior to the bladder before passing below the pubic symphysis (see [link]**b**). The length of the male urethra varies between men but averages 20 cm in length. It is divided into four regions: the preprostatic urethra, the prostatic urethra, the membranous urethra, and the spongy or penile urethra. The preprostatic urethra is very short and incorporated into the bladder wall. The prostatic urethra passes through the prostate gland. During sexual intercourse, it receives sperm via the ejaculatory ducts and secretions from the seminal vesicles. Paired Cowper's glands (bulbourethral glands) produce and secrete mucus into the urethra to buffer urethral pH during sexual stimulation. The mucus neutralizes the usually acidic environment and lubricates the urethra, decreasing the resistance to ejaculation. The membranous urethra passes through the deep muscles of the perineum, where it is invested by the overlying urethral sphincters. The spongy urethra exits at the tip (external urethral orifice) of the penis after passing through the corpus spongiosum. Mucous glands are found along much of the length of the urethra and protect the urethra from extremes of urine pH. Innervation is the same in both males and females.

Bladder

The urinary bladder collects urine from both ureters ([link]). The bladder lies anterior to the uterus in females, posterior to the pubic bone and anterior to the rectum. During late pregnancy, its capacity is reduced due to compression by the enlarging uterus, resulting in increased frequency of urination. In males, the anatomy is similar, minus the uterus, and with the addition of the prostate inferior to the bladder. The bladder is partially **retroperitoneal** (outside the peritoneal cavity) with its peritoneal-covered "dome" projecting into the abdomen when the bladder is distended with urine.

Bladder



(a) Anterior cross section of the bladder. (b) The detrusor muscle of the bladder (source: monkey tissue) LM × 448. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

Note:

View the University of Michigan WebScope to explore the tissue sample in greater detail.

The bladder is a highly distensible organ comprised of irregular crisscrossing bands of smooth muscle collectively called the **detrusor muscle**. The interior surface is made of transitional cellular epithelium that is structurally suited for the large volume fluctuations of the bladder. When empty, it resembles columnar epithelia, but when stretched, it “transitions” (hence the name) to a squamous appearance (see [link]). Volumes in adults can range from nearly zero to 500–600 mL.

The detrusor muscle contracts with significant force in the young. The bladder’s strength diminishes with age, but voluntary contractions of abdominal skeletal muscles can increase intra-abdominal pressure to promote more forceful bladder emptying. Such voluntary contraction is also used in forceful defecation and childbirth.

Micturition Reflex

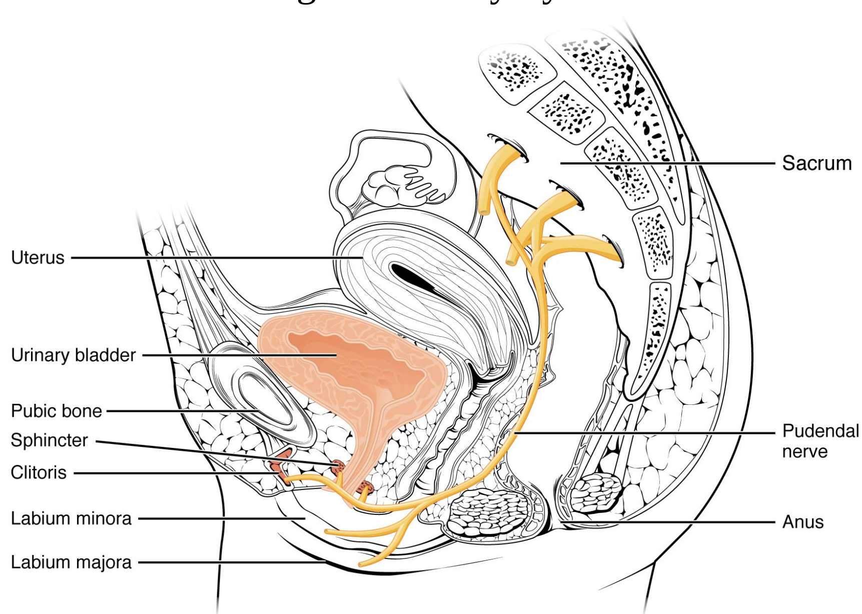
Micturition is a less-often used, but proper term for urination or voiding. It results from an interplay of involuntary and voluntary actions by the internal and external urethral sphincters. When bladder volume reaches about 150 mL, an urge to void is sensed but is easily overridden. Voluntary control of urination relies on consciously preventing relaxation of the external urethral sphincter to maintain urinary continence. As the bladder fills, subsequent urges become harder to ignore. Ultimately, voluntary constraint fails with resulting **incontinence**, which will occur as bladder volume approaches 300 to 400 mL.

Normal micturition is a result of stretch receptors in the bladder wall that transmit nerve impulses to the sacral region of the spinal cord to generate a spinal reflex. The resulting parasympathetic neural outflow causes contraction of the detrusor muscle and relaxation of the involuntary internal urethral sphincter. At the same time, the spinal cord inhibits somatic motor neurons, resulting in the relaxation of the skeletal muscle of the external urethral sphincter. The micturition reflex is active in infants but with maturity, children learn to override the reflex by asserting external sphincter control, thereby delaying voiding (potty training). This reflex may be preserved even in the face of spinal cord injury that results in paraplegia or

quadriplegia. However, relaxation of the external sphincter may not be possible in all cases, and therefore, periodic catheterization may be necessary for bladder emptying.

Nerves involved in the control of urination include the hypogastric, pelvic, and pudendal ([link]). Voluntary micturition requires an intact spinal cord and functional pudendal nerve arising from the **sacral micturition center**. Since the external urinary sphincter is voluntary skeletal muscle, actions by cholinergic neurons maintain contraction (and thereby continence) during filling of the bladder. At the same time, sympathetic nervous activity via the hypogastric nerves suppresses contraction of the detrusor muscle. With further bladder stretch, afferent signals traveling over sacral pelvic nerves activate parasympathetic neurons. This activates efferent neurons to release acetylcholine at the neuromuscular junctions, producing detrusor contraction and bladder emptying.

Nerves Innervating the Urinary System



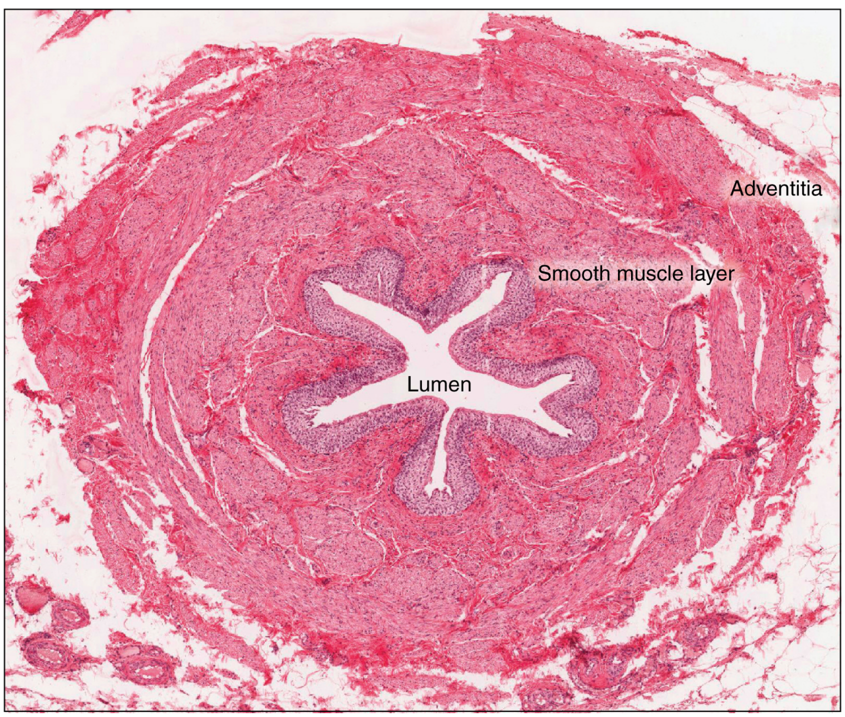
Ureters

The kidneys and ureters are completely retroperitoneal, and the bladder has a peritoneal covering only over the dome. As urine is formed, it drains into the calyces of the kidney, which merge to form the funnel-shaped renal pelvis in the hilum of each kidney. The renal pelvis narrows to become the

ureter of each kidney. As urine passes through the ureter, it does not passively drain into the bladder but rather is propelled by waves of peristalsis. As the ureters enter the pelvis, they sweep laterally, hugging the pelvic walls. As they approach the bladder, they turn medially and pierce the bladder wall obliquely. This is important because it creates an one-way valve (a **physiological sphincter** rather than an **anatomical sphincter**) that allows urine into the bladder but prevents reflux of urine from the bladder back into the ureter. Children born lacking this oblique course of the ureter through the bladder wall are susceptible to “vesicoureteral reflux,” which dramatically increases their risk of serious UTI. Pregnancy also increases the likelihood of reflux and UTI.

The ureters are approximately 30 cm long. The inner mucosa is lined with transitional epithelium ([link]) and scattered goblet cells that secrete protective mucus. The muscular layer of the ureter consists of longitudinal and circular smooth muscles that create the peristaltic contractions to move the urine into the bladder without the aid of gravity. Finally, a loose adventitial layer composed of collagen and fat anchors the ureters between the parietal peritoneum and the posterior abdominal wall.

Ureter



Peristaltic contractions help to move urine

through the lumen with contributions from fluid pressure and gravity. LM × 128. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

Chapter Review

The urethra is the only urinary structure that differs significantly between males and females. This is due to the dual role of the male urethra in transporting both urine and semen. The urethra arises from the trigone area at the base of the bladder. Urination is controlled by an involuntary internal sphincter of smooth muscle and a voluntary external sphincter of skeletal muscle. The shorter female urethra contributes to the higher incidence of bladder infections in females. The male urethra receives secretions from the prostate gland, Cowper’s gland, and seminal vesicles as well as sperm. The bladder is largely retroperitoneal and can hold up to 500–600 mL urine. Micturition is the process of voiding the urine and involves both involuntary and voluntary actions. Voluntary control of micturition requires a mature and intact sacral micturition center. It also requires an intact spinal cord. Loss of control of micturition is called incontinence and results in voiding when the bladder contains about 250 mL urine. The ureters are retroperitoneal and lead from the renal pelvis of the kidney to the trigone area at the base of the bladder. A thick muscular wall consisting of longitudinal and circular smooth muscle helps move urine toward the bladder by way of peristaltic contractions.

Review Questions

Exercise:

Problem: Peristaltic contractions occur in the ________.

a. urethra
b. bladder

c. ureters
d. urethra, bladder, and ureters

Solution:

C

Exercise:

Problem:

Somatic motor neurons must be _________ to relax the external urethral sphincter to allow urination.

a. stimulated
b. inhibited

Solution:

B

Exercise:

Problem:

Which part of the urinary system is *not* completely retroperitoneal?

a. kidneys
b. ureters
c. bladder
d. nephrons

Solution:

C

Critical Thinking Questions

Exercise:

Problem:

Why are females more likely to contract bladder infections than males?

Solution:

The longer urethra of males means bacteria must travel farther to the bladder to cause an infection.

Exercise:

Problem: Describe how forceful urination is accomplished.

Solution:

Forceful urination is accomplished by contraction of abdominal muscles.

Glossary

anatomical sphincter
: smooth or skeletal muscle surrounding the lumen of a vessel or hollow organ that can restrict flow when contracted

detrusor muscle
: smooth muscle in the bladder wall; fibers run in all directions to reduce the size of the organ when emptying it of urine

external urinary sphincter
: skeletal muscle; must be relaxed consciously to void urine

internal urinary sphincter
: smooth muscle at the juncture of the bladder and urethra; relaxes as the bladder fills to allow urine into the urethra

incontinence
: loss of ability to control micturition

micturition
: also called urination or voiding

physiological sphincter
: sphincter consisting of circular smooth muscle indistinguishable from adjacent muscle but possessing differential innervations, permitting its function as a sphincter; structurally weak

retroperitoneal
: outside the peritoneal cavity; in the case of the kidney and ureters, between the parietal peritoneum and the abdominal wall

sacral micturition center
: group of neurons in the sacral region of the spinal cord that controls urination; acts reflexively unless its action is modified by higher brain centers to allow voluntary urination

trigone
: area at the base of the bladder marked by the two ureters in the posterior–lateral aspect and the urethral orifice in the anterior aspect oriented like points on a triangle

urethra
: transports urine from the bladder to the outside environment

Gross Anatomy of the Kidney

By the end of this section, you will be able to:

- Describe the external structure of the kidney, including its location, support structures, and covering
- Identify the major internal divisions and structures of the kidney
- Identify the major blood vessels associated with the kidney and trace the path of blood through the kidney
- Compare and contrast the cortical and juxtamedullary nephrons
- Name structures found in the cortex and medulla
- Describe the physiological characteristics of the cortex and medulla

The kidneys lie on either side of the spine in the retroperitoneal space between the parietal peritoneum and the posterior abdominal wall, well protected by muscle, fat, and ribs. They are roughly the size of your fist, and the male kidney is typically a bit larger than the female kidney. The kidneys are well vascularized, receiving about 25 percent of the cardiac output at rest.

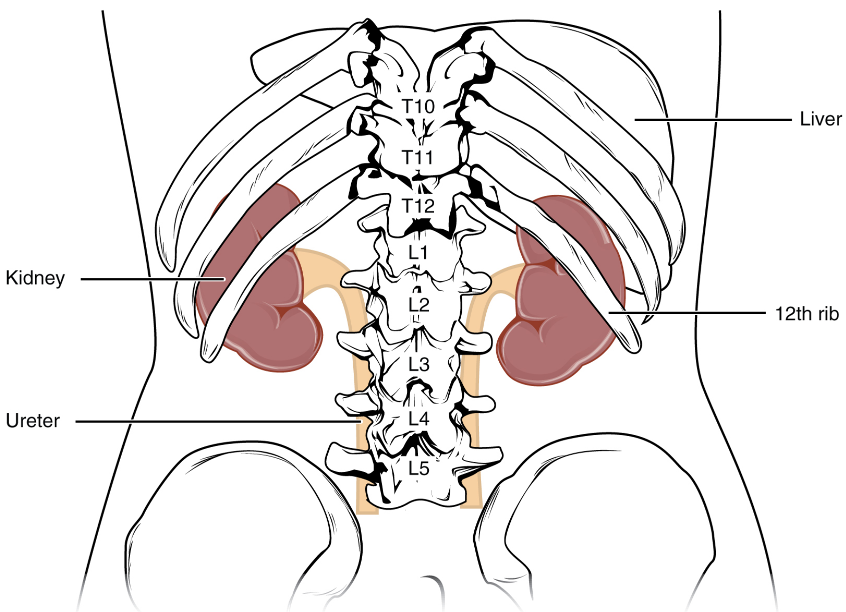
Note:

There have never been sufficient kidney donations to provide a kidney to each person needing one. Watch this video to learn about the TED (Technology, Entertainment, Design) Conference held in March 2011. In this video, Dr. Anthony Atala discusses a cutting-edge technique in which a new kidney is “printed.” The successful utilization of this technology is still several years in the future, but imagine a time when you can print a replacement organ or tissue on demand.

External Anatomy

The left kidney is located at about the T12 to L3 vertebrae, whereas the right is lower due to slight displacement by the liver. Upper portions of the kidneys are somewhat protected by the eleventh and twelfth ribs ([link]). Each kidney weighs about 125–175 g in males and 115–155 g in females. They are about 11–14 cm in length, 6 cm wide, and 4 cm thick, and are directly covered by a fibrous capsule composed of dense, irregular connective tissue that helps to hold their shape and protect them. This capsule is covered by a shock-absorbing layer of adipose tissue called the **renal fat pad**, which in turn is encompassed by a tough renal fascia. The fascia and, to a lesser extent, the overlying peritoneum serve to firmly anchor the kidneys to the posterior abdominal wall in a retroperitoneal position.

Kidneys



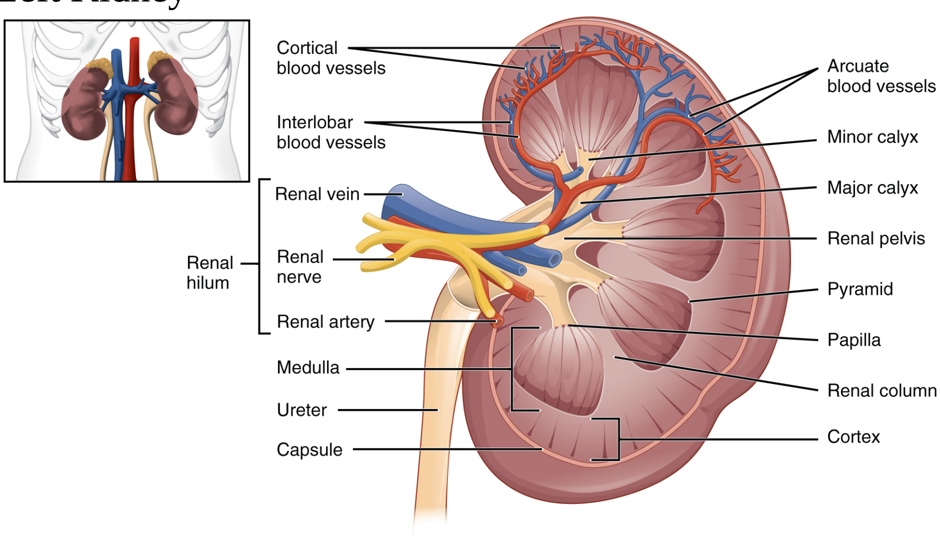
The kidneys are slightly protected by the ribs and are surrounded by fat for protection (not shown).

On the superior aspect of each kidney is the adrenal gland. The adrenal cortex directly influences renal function through the production of the hormone aldosterone to stimulate sodium reabsorption.

Internal Anatomy

A frontal section through the kidney reveals an outer region called the **renal cortex** and an inner region called the **medulla** ([link]). The **renal columns** are connective tissue extensions that radiate downward from the cortex through the medulla to separate the most characteristic features of the medulla, the **renal pyramids** and **renal papillae**. The papillae are bundles of collecting ducts that transport urine made by nephrons to the **calyces** of the kidney for excretion. The renal columns also serve to divide the kidney into 6–8 lobes and provide a supportive framework for vessels that enter and exit the cortex. The pyramids and renal columns taken together constitute the kidney lobes.

Left Kidney



Renal Hilum

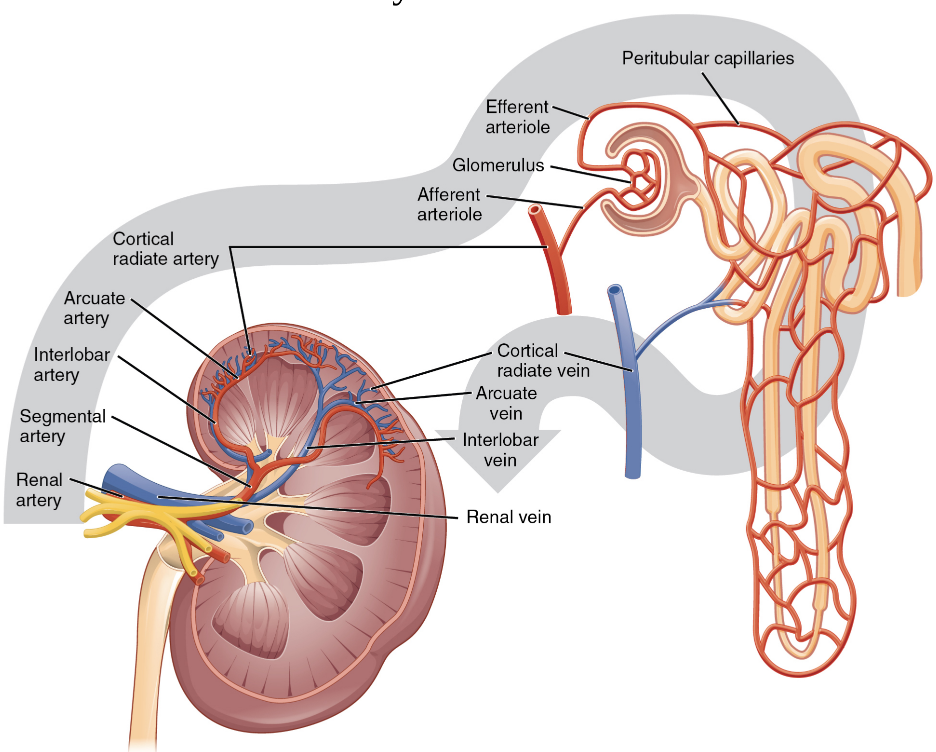
The **renal hilum** is the entry and exit site for structures servicing the kidneys: vessels, nerves, lymphatics, and ureters. The medial-facing hila are tucked into the sweeping convex outline of the cortex. Emerging from the hilum is the renal pelvis, which is formed from the major and minor calyxes

in the kidney. The smooth muscle in the renal pelvis funnels urine via peristalsis into the ureter. The renal arteries form directly from the descending aorta, whereas the renal veins return cleansed blood directly to the inferior vena cava. The artery, vein, and renal pelvis are arranged in an anterior-to-posterior order.

Nephrons and Vessels

The renal artery first divides into segmental arteries, followed by further branching to form interlobar arteries that pass through the renal columns to reach the cortex ([link]). The interlobar arteries, in turn, branch into arcuate arteries, cortical radiate arteries, and then into afferent arterioles. The afferent arterioles service about 1.3 million nephrons in each kidney.

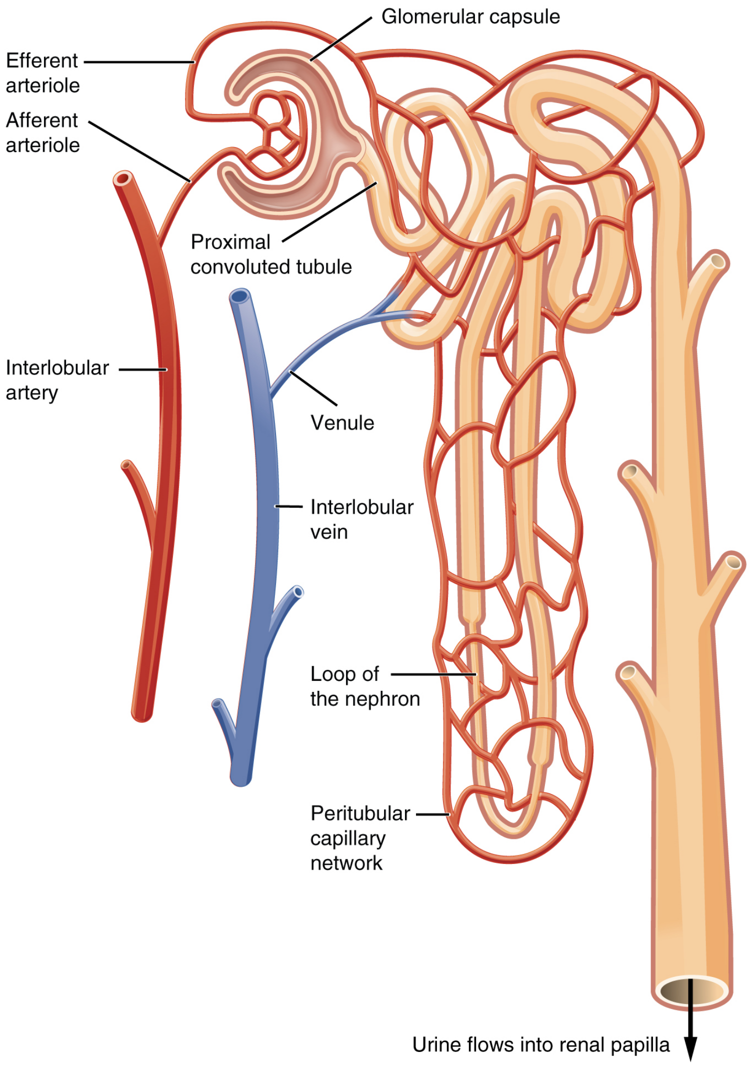
Blood Flow in the Kidney



Nephrons are the “functional units” of the kidney; they cleanse the blood and balance the constituents of the circulation. The afferent arterioles form a tuft of high-pressure capillaries about 200 µm in diameter, the **glomerulus**. The rest of the nephron consists of a continuous sophisticated

tubule whose proximal end surrounds the glomerulus in an intimate embrace—this is **Bowman’s capsule**. The glomerulus and Bowman’s capsule together form the **renal corpuscle**. As mentioned earlier, these glomerular capillaries filter the blood based on particle size. After passing through the renal corpuscle, the capillaries form a second arteriole, the **efferent arteriole** ([link]). These will next form a capillary network around the more distal portions of the nephron tubule, the **peritubular capillaries** and **vasa recta**, before returning to the venous system. As the glomerular filtrate progresses through the nephron, these capillary networks recover most of the solutes and water, and return them to the circulation. Since a capillary bed (the glomerulus) drains into a vessel that in turn forms a second capillary bed, the definition of a portal system is met. This is the only portal system in which an arteriole is found between the first and second capillary beds. (Portal systems also link the hypothalamus to the anterior pituitary, and the blood vessels of the digestive viscera to the liver.)

Blood Flow in the Nephron



The two capillary beds are clearly shown in this figure. The efferent arteriole is the connecting vessel between the glomerulus and the peritubular capillaries and vasa recta.

Note:

Visit this link to view an interactive tutorial of the flow of blood through the kidney.

Cortex

In a dissected kidney, it is easy to identify the cortex; it appears lighter in color compared to the rest of the kidney. All of the renal corpuscles as well as both the **proximal convoluted tubules (PCTs)** and **distal convoluted tubules** are found here. Some nephrons have a short **loop of Henle** that does not dip beyond the cortex. These nephrons are called **cortical nephrons**. About 15 percent of nephrons have long loops of Henle that extend deep into the medulla and are called **juxtamedullary nephrons**.

Chapter Review

As noted previously, the structure of the kidney is divided into two principle regions—the peripheral rim of cortex and the central medulla. The two kidneys receive about 25 percent of cardiac output. They are protected in the retroperitoneal space by the renal fat pad and overlying ribs and muscle. Ureters, blood vessels, lymph vessels, and nerves enter and leave at the renal hilum. The renal arteries arise directly from the aorta, and the renal veins drain directly into the inferior vena cava. Kidney function is derived from the actions of about 1.3 million nephrons per kidney; these are the “functional units.” A capillary bed, the glomerulus, filters blood and the filtrate is captured by Bowman’s capsule. A portal system is formed when the blood flows through a second capillary bed surrounding the proximal and distal convoluted tubules and the loop of Henle. Most water and solutes are recovered by this second capillary bed. This filtrate is processed and finally gathered by collecting ducts that drain into the minor calyces, which

merge to form major calyces; the filtrate then proceeds to the renal pelvis and finally the ureters.

Review Questions

Exercise:

Problem:

The renal pyramids are separated from each other by extensions of the renal cortex called _________.

a. renal medulla
b. minor calyces
c. medullary cortices
d. renal columns

Solution:

D

Exercise:

Problem:

The primary structure found within the medulla is the _________.

a. loop of Henle
b. minor calyces
c. portal system
d. ureter

Solution:

A

Exercise:

Problem: The right kidney is slightly lower because ________.

a. it is displaced by the liver
b. it is displace by the heart
c. it is slightly smaller
d. it needs protection of the lower ribs

Solution:

A

Critical Thinking Questions

Exercise:

Problem: What anatomical structures provide protection to the kidney?

Solution:

Retroperitoneal anchoring, renal fat pads, and ribs provide protection to the kidney.

Exercise:

Problem:

How does the renal portal system differ from the hypothalamo–hypophyseal and digestive portal systems?

Solution:

The renal portal system has an artery between the first and second capillary bed. The others have a vein.

Exercise:

Problem: Name the structures found in the renal hilum.

Solution:

The structures found in the renal hilum are arteries, veins, ureters, lymphatics, and nerves.

Glossary

Bowman's capsule
: cup-shaped sack lined by a simple squamous epithelium (parietal surface) and specialized cells called podocytes (visceral surface) that participate in the filtration process; receives the filtrate which then passes on to the PCTs

calyces
: cup-like structures receiving urine from the collecting ducts where it passes on to the renal pelvis and ureter

cortical nephrons
: nephrons with loops of Henle that do not extend into the renal medulla

distal convoluted tubules
: portions of the nephron distal to the loop of Henle that receive hyposmotic filtrate from the loop of Henle and empty into collecting ducts

efferent arteriole
: arteriole carrying blood from the glomerulus to the capillary beds around the convoluted tubules and loop of Henle; portion of the portal system

glomerulus
: tuft of capillaries surrounded by Bowman's capsule; filters the blood based on size

juxtamedullary nephrons
: nephrons adjacent to the border of the cortex and medulla with loops of Henle that extend into the renal medulla

loop of Henle
: descending and ascending portions between the proximal and distal convoluted tubules; those of cortical nephrons do not extend into the medulla, whereas those of juxtamedullary nephrons do extend into the medulla

nephrons
: functional units of the kidney that carry out all filtration and modification to produce urine; consist of renal corpuscles, proximal and distal convoluted tubules, and descending and ascending loops of Henle; drain into collecting ducts

medulla
: inner region of kidney containing the renal pyramids

peritubular capillaries
: second capillary bed of the renal portal system; surround the proximal and distal convoluted tubules; associated with the vasa recta

proximal convoluted tubules (PCTs)
: tortuous tubules receiving filtrate from Bowman’s capsule; most active part of the nephron in reabsorption and secretion

renal columns
: extensions of the renal cortex into the renal medulla; separates the renal pyramids; contains blood vessels and connective tissues

renal corpuscle
: consists of the glomerulus and Bowman’s capsule

renal cortex
: outer part of kidney containing all of the nephrons; some nephrons have loops of Henle extending into the medulla

renal fat pad

adipose tissue between the renal fascia and the renal capsule that provides protective cushioning to the kidney

renal hilum

recessed medial area of the kidney through which the renal artery, renal vein, ureters, lymphatics, and nerves pass

renal papillae

medullary area of the renal pyramids where collecting ducts empty urine into the minor calyces

renal pyramids

six to eight cone-shaped tissues in the medulla of the kidney containing collecting ducts and the loops of Henle of juxtamedullary nephrons

vasa recta

branches of the efferent arterioles that parallel the course of the loops of Henle and are continuous with the peritubular capillaries; with the glomerulus, form a portal system

Microscopic Anatomy of the Kidney
By the end of this section, you will be able to:

- Distinguish the histological differences between the renal cortex and medulla
- Describe the structure of the filtration membrane
- Identify the major structures and subdivisions of the renal corpuscles, renal tubules, and renal capillaries
- Discuss the function of the peritubular capillaries and vasa recta
- Identify the location of the juxtaglomerular apparatus and describe the cells that line it
- Describe the histology of the proximal convoluted tubule, loop of Henle, distal convoluted tubule, and collecting ducts

The renal structures that conduct the essential work of the kidney cannot be seen by the naked eye. Only a light or electron microscope can reveal these structures. Even then, serial sections and computer reconstruction are necessary to give us a comprehensive view of the functional anatomy of the nephron and its associated blood vessels.

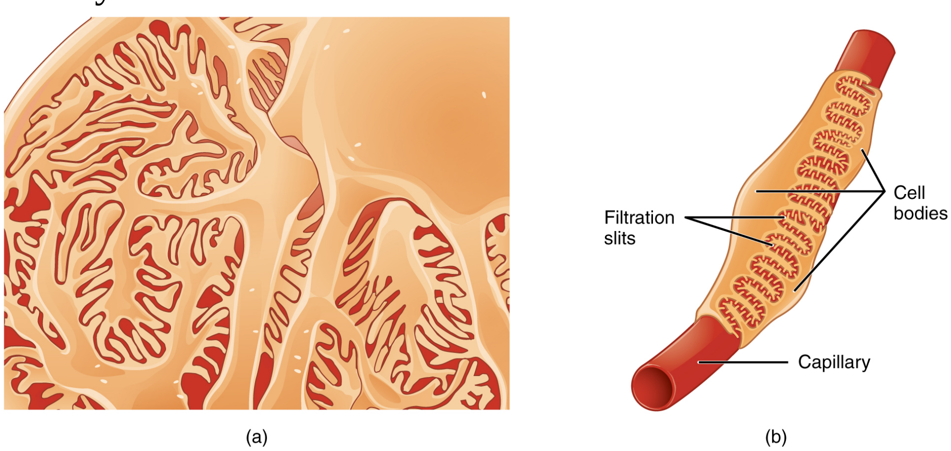
Nephrons: The Functional Unit

Nephrons take a simple filtrate of the blood and modify it into urine. Many changes take place in the different parts of the nephron before urine is created for disposal. The term **forming urine** will be used hereafter to describe the filtrate as it is modified into true urine. The principle task of the nephron population is to balance the plasma to homeostatic set points and excrete potential toxins in the urine. They do this by accomplishing three principle functions—filtration, reabsorption, and secretion. They also have additional secondary functions that exert control in three areas: blood pressure (via production of **renin**), red blood cell production (via the hormone EPO), and calcium absorption (via conversion of calcidiol into calcitriol, the active form of vitamin D).

Renal Corpuscle

As discussed earlier, the renal corpuscle consists of a tuft of capillaries called the glomerulus that is largely surrounded by Bowman's (glomerular) capsule. The glomerulus is a high-pressure capillary bed between afferent and efferent arterioles. Bowman's capsule surrounds the glomerulus to form a lumen, and captures and directs this filtrate to the PCT. The outermost part of Bowman's capsule, the parietal layer, is a simple squamous epithelium. It transitions onto the glomerular capillaries in an intimate embrace to form the visceral layer of the capsule. Here, the cells are not squamous, but uniquely shaped cells (**podocytes**) extending finger-like arms (**pedicels**) to cover the glomerular capillaries ([link]). These projections interdigitate to form **filtration slits**, leaving small gaps between the digits to form a sieve. As blood passes through the glomerulus, 10 to 20 percent of the plasma filters between these sieve-like fingers to be captured by Bowman's capsule and funneled to the PCT. Where the fenestrae (windows) in the glomerular capillaries match the spaces between the podocyte "fingers," the only thing separating the capillary lumen and the lumen of Bowman's capsule is their shared basement membrane ([link]). These three features comprise what is known as the filtration membrane. This membrane permits very rapid movement of filtrate from capillary to capsule though pores that are only 70 nm in diameter.

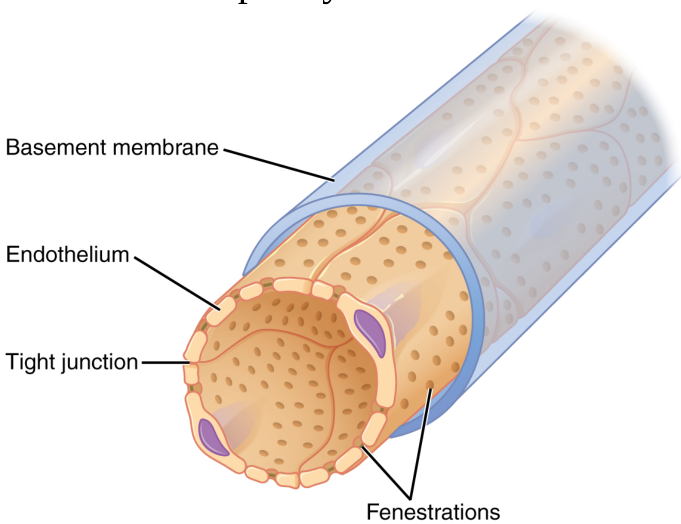
Podocytes



Podocytes interdigitate with structures called pedicels and filter substances in a way similar to fenestrations. In (a), the large cell body can be seen at the top right corner, with branches extending from the cell body. The smallest finger-like extensions are the pedicels.

Pedicels on one podocyte always interdigitate with the pedicels of another podocyte. (b) This capillary has three podocytes wrapped around it.

Fenestrated Capillary



Fenestrations allow many substances to diffuse from the blood based primarily on size.

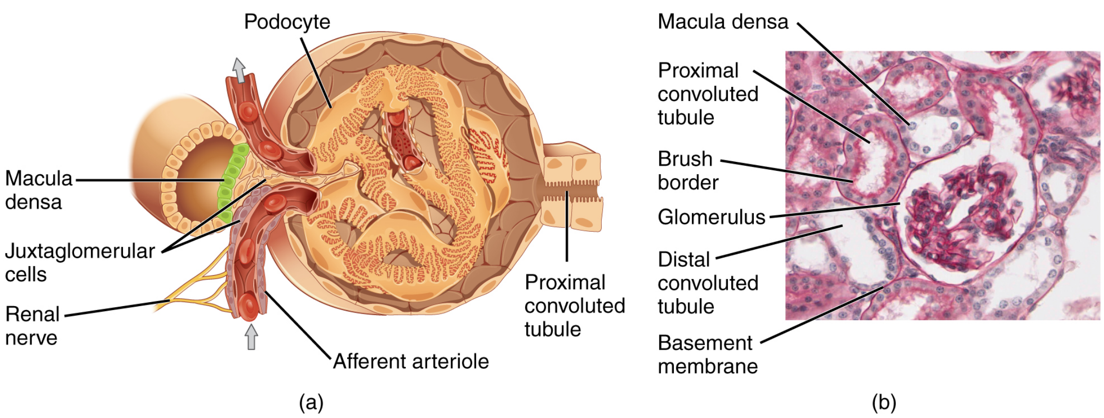
The **fenestrations** prevent filtration of blood cells or large proteins, but allow most other constituents through. These substances cross readily if they are less than 4 nm in size and most pass freely up to 8 nm in size. An additional factor affecting the ability of substances to cross this barrier is their electric charge. The proteins associated with these pores are negatively charged, so they tend to repel negatively charged substances and allow positively charged substances to pass more readily. The basement membrane prevents filtration of medium-to-large proteins such as globulins. There are also **mesangial** cells in the filtration membrane that can contract to help regulate the rate of filtration of the glomerulus. Overall, filtration is regulated by fenestrations in capillary endothelial cells, podocytes with filtration slits, membrane charge, and the basement membrane between

capillary cells. The result is the creation of a filtrate that does not contain cells or large proteins, and has a slight predominance of positively charged substances.

Lying just outside Bowman's capsule and the glomerulus is the **juxtaglomerular apparatus (JGA)** ([link]). At the juncture where the afferent and efferent arterioles enter and leave Bowman's capsule, the initial part of the distal convoluted tubule (DCT) comes into direct contact with the arterioles. The wall of the DCT at that point forms a part of the JGA known as the **macula densa**. This cluster of cuboidal epithelial cells monitors the fluid composition of fluid flowing through the DCT. In response to the concentration of Na^+ in the fluid flowing past them, these cells release paracrine signals. They also have a single, nonmotile cilium that responds to the rate of fluid movement in the tubule. The paracrine signals released in response to changes in flow rate and Na^+ concentration are adenosine triphosphate (ATP) and adenosine.

Juxtaglomerular Apparatus and Glomerulus

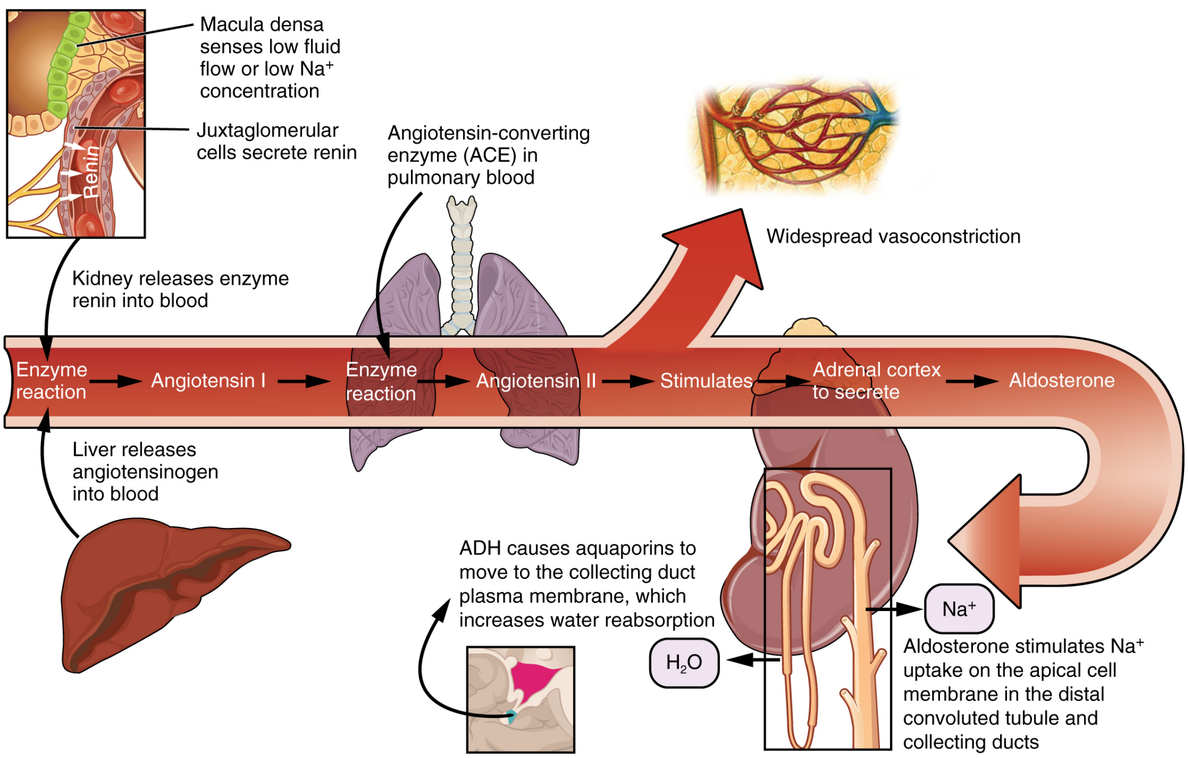
(a) The JGA allows specialized cells to monitor the composition of the fluid in the DCT and adjust the glomerular filtration rate. (b) This micrograph shows the glomerulus and surrounding structures. LM × 1540. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)



A second cell type in this apparatus is the **juxtaglomerular cell**. This is a modified, smooth muscle cell lining the afferent arteriole that can contract or relax in response to ATP or adenosine released by the macula densa. Such contraction and relaxation regulate blood flow to the glomerulus. If

the osmolarity of the filtrate is too high (hyperosmotic), the juxtaglomerular cells will contract, decreasing the glomerular filtration rate (GFR) so less plasma is filtered, leading to less urine formation and greater retention of fluid. This will ultimately decrease blood osmolarity toward the physiologic norm. If the osmolarity of the filtrate is too low, the juxtaglomerular cells will relax, increasing the GFR and enhancing the loss of water to the urine, causing blood osmolarity to rise. In other words, when osmolarity goes up, filtration and urine formation decrease and water is retained. When osmolarity goes down, filtration and urine formation increase and water is lost by way of the urine. The net result of these opposing actions is to keep the rate of filtration relatively constant. A second function of the macula densa cells is to regulate renin release from the juxtaglomerular cells of the afferent arteriole ([link]). Active renin is a protein comprised of 304 amino acids that cleaves several amino acids from **angiotensinogen** to produce **angiotensin I**. Angiotensin I is not biologically active until converted to angiotensin II by **angiotensin-converting enzyme (ACE)** from the lungs. **Angiotensin II** is a systemic vasoconstrictor that helps to regulate blood pressure by increasing it. Angiotensin II also stimulates the release of the steroid hormone aldosterone from the adrenal cortex. Aldosterone stimulates Na^+ reabsorption by the kidney, which also results in water retention and increased blood pressure.

Conversion of Angiotensin I to Angiotensin II



The enzyme renin converts the pro-enzyme angiotensin I; the lung-derived enzyme ACE converts angiotensin I into active angiotensin II.

Proximal Convoluted Tubule (PCT)

Filtered fluid collected by Bowman's capsule enters into the PCT. It is called convoluted due to its tortuous path. Simple cuboidal cells form this tubule with prominent microvilli on the luminal surface, forming a **brush border**. These microvilli create a large surface area to maximize the absorption and secretion of solutes (Na^+, Cl^-, glucose, etc.), the most essential function of this portion of the nephron. These cells actively transport ions across their membranes, so they possess a high concentration of mitochondria in order to produce sufficient ATP.

Loop of Henle

The descending and ascending portions of the loop of Henle (sometimes referred to as the nephron loop) are, of course, just continuations of the same tubule. They run adjacent and parallel to each other after having made a hairpin turn at the deepest point of their descent. The descending loop of Henle consists of an initial short, thick portion and long, thin portion, whereas the ascending loop consists of an initial short, thin portion followed by a long, thick portion. The descending thick portion consists of simple cuboidal epithelium similar to that of the PCT. The descending and ascending thin portions consists of simple squamous epithelium. As you will see later, these are important differences, since different portions of the loop have different permeabilities for solutes and water. The ascending thick portion consists of simple cuboidal epithelium similar to the DCT.

Distal Convoluted Tubule (DCT)

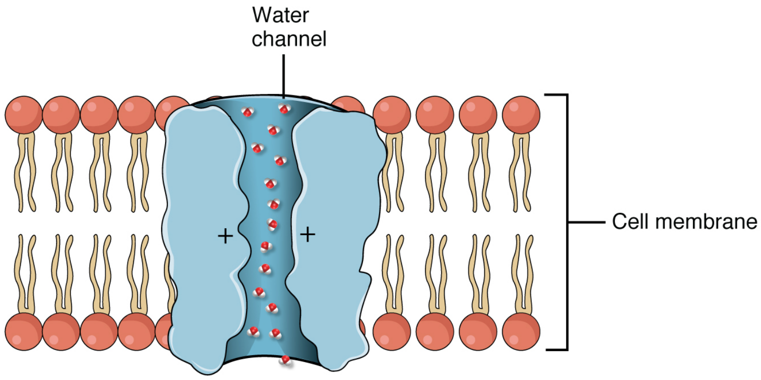
The DCT, like the PCT, is very tortuous and formed by simple cuboidal epithelium, but it is shorter than the PCT. These cells are not as active as those in the PCT; thus, there are fewer microvilli on the apical surface. However, these cells must also pump ions against their concentration gradient, so you will find of large numbers of mitochondria, although fewer than in the PCT.

Collecting Ducts

The collecting ducts are continuous with the nephron but not technically part of it. In fact, each duct collects filtrate from several nephrons for final modification. Collecting ducts merge as they descend deeper in the medulla to form about 30 terminal ducts, which empty at a papilla. They are lined with simple squamous epithelium with receptors for ADH. When stimulated by ADH, these cells will insert **aquaporin** channel proteins into their membranes, which as their name suggests, allow water to pass from the duct lumen through the cells and into the interstitial spaces to be

recovered by the vasa recta. This process allows for the recovery of large amounts of water from the filtrate back into the blood. In the absence of ADH, these channels are not inserted, resulting in the excretion of water in the form of dilute urine. Most, if not all, cells of the body contain aquaporin molecules, whose channels are so small that only water can pass. At least 10 types of aquaporins are known in humans, and six of those are found in the kidney. The function of all aquaporins is to allow the movement of water across the lipid-rich, hydrophobic cell membrane ([link]).

Aquaporin Water Channel



Positive charges inside the channel prevent the leakage of electrolytes across the cell membrane, while allowing water to move due to osmosis.

Chapter Review

The functional unit of the kidney, the nephron, consists of the renal corpuscle, PCT, loop of Henle, and DCT. Cortical nephrons have short loops of Henle, whereas juxtamedullary nephrons have long loops of Henle extending into the medulla. About 15 percent of nephrons are juxtamedullary. The glomerulus is a capillary bed that filters blood principally based on particle size. The filtrate is captured by Bowman’s capsule and directed to the PCT. A filtration membrane is formed by the fused basement membranes of the podocytes and the capillary endothelial cells that they embrace. Contractile mesangial cells further perform a role in

regulating the rate at which the blood is filtered. Specialized cells in the JGA produce paracrine signals to regulate blood flow and filtration rates of the glomerulus. Other JGA cells produce the enzyme renin, which plays a central role in blood pressure regulation. The filtrate enters the PCT where absorption and secretion of several substances occur. The descending and ascending limbs of the loop of Henle consist of thick and thin segments. Absorption and secretion continue in the DCT but to a lesser extent than in the PCT. Each collecting duct collects forming urine from several nephrons and responds to the posterior pituitary hormone ADH by inserting aquaporin water channels into the cell membrane to fine tune water recovery.

Review Questions

Exercise:

Problem: Blood filtrate is captured in the lumen of the ________.

a. glomerulus
b. Bowman’s capsule
c. calyces
d. renal papillae

Solution:

B

Exercise:

Problem:

What are the names of the capillaries following the efferent arteriole?

a. arcuate and medullary
b. interlobar and interlobular
c. peritubular and vasa recta
d. peritubular and medullary

Solution:

C

Exercise:

Problem: The functional unit of the kidney is called ________.

a. the renal hilus
b. the renal corpuscle
c. the nephron
d. Bowman’s capsule

Solution:

C

Critical Thinking Questions

Exercise:

Problem: Which structures make up the renal corpuscle?

Solution:

The structures that make up the renal corpuscle are the glomerulus, Bowman’s capsule, and PCT.

Exercise:

Problem:

What are the major structures comprising the filtration membrane?

Solution:

The major structures comprising the filtration membrane are fenestrations and podocyte fenestra, fused basement membrane, and filtration slits.

Glossary

angiotensin-converting enzyme (ACE)
: enzyme produced by the lungs that catalyzes the reaction of inactive angiotensin I into active angiotensin II

angiotensin I
: protein produced by the enzymatic action of renin on angiotensinogen; inactive precursor of angiotensin II

angiotensin II
: protein produced by the enzymatic action of ACE on inactive angiotensin I; actively causes vasoconstriction and stimulates aldosterone release by the adrenal cortex

angiotensinogen
: inactive protein in the circulation produced by the liver; precursor of angiotensin I; must be modified by the enzymes renin and ACE to be activated

aquaporin
: protein-forming water channels through the lipid bilayer of the cell; allows water to cross; activation in the collecting ducts is under the control of ADH

brush border
: formed by microvilli on the surface of certain cuboidal cells; in the kidney it is found in the PCT; increases surface area for absorption in the kidney

fenestrations
: small windows through a cell, allowing rapid filtration based on size; formed in such a way as to allow substances to cross through a cell

without mixing with cell contents

filtration slits
formed by pedicels of podocytes; substances filter between the pedicels based on size

forming urine
filtrate undergoing modifications through secretion and reabsorption before true urine is produced

juxtaglomerular apparatus (JGA)
located at the juncture of the DCT and the afferent and efferent arterioles of the glomerulus; plays a role in the regulation of renal blood flow and GFR

juxtaglomerular cell
modified smooth muscle cells of the afferent arteriole; secretes renin in response to a drop in blood pressure

macula densa
cells found in the part of the DCT forming the JGA; sense Na^+ concentration in the forming urine

mesangial
contractile cells found in the glomerulus; can contract or relax to regulate filtration rate

pedicels
finger-like projections of podocytes surrounding glomerular capillaries; interdigitate to form a filtration membrane

podocytes
cells forming finger-like processes; form the visceral layer of Bowman's capsule; pedicels of the podocytes interdigitate to form a filtration membrane

renin

enzyme produced by juxtaglomerular cells in response to decreased blood pressure or sympathetic nervous activity; catalyzes the conversion of angiotensinogen into angiotensin I

Physiology of Urine Formation
By the end of this section, you will be able to:

- Describe the hydrostatic and colloid osmotic forces that favor and oppose filtration
- Describe glomerular filtration rate (GFR), state the average value of GFR, and explain how clearance rate can be used to measure GFR
- Predict specific factors that will increase or decrease GFR
- State the percent of the filtrate that is normally reabsorbed and explain why the process of reabsorption is so important
- Calculate daily urine production
- List common symptoms of kidney failure

Having reviewed the anatomy and microanatomy of the urinary system, now is the time to focus on the physiology. You will discover that different parts of the nephron utilize specific processes to produce urine: filtration, reabsorption, and secretion. You will learn how each of these processes works and where they occur along the nephron and collecting ducts. The physiologic goal is to modify the composition of the plasma and, in doing so, produce the waste product urine.

Failure of the renal anatomy and/or physiology can lead suddenly or gradually to renal failure. In this event, a number of symptoms, signs, or laboratory findings point to the diagnosis ([link]).

Symptoms of Kidney Failure
Weakness
Lethargy
Shortness of breath

Symptoms of Kidney Failure
Widespread edema
Anemia
Metabolic acidosis
Metabolic alkalosis
Heart arrhythmias
Uremia (high urea level in the blood)
Loss of appetite
Fatigue
Excessive urination
Oliguria (too little urine output)

Glomerular Filtration Rate (GFR)

The volume of filtrate formed by both kidneys per minute is termed the **glomerular filtration rate (GFR)**. The heart pumps about 5 L blood per min under resting conditions. Approximately 20 percent or one liter enters the kidneys to be filtered. On average, this liter results in the production of about 125 mL/min filtrate produced in men (range of 90 to 140 mL/min) and 105 mL/min filtrate produced in women (range of 80 to 125 mL/min). This amount equates to a volume of about 180 L/day in men and 150 L/day in women. Ninety-nine percent of this filtrate is returned to the circulation by reabsorption so that only about 1–2 liters of urine are produced per day ([link]).

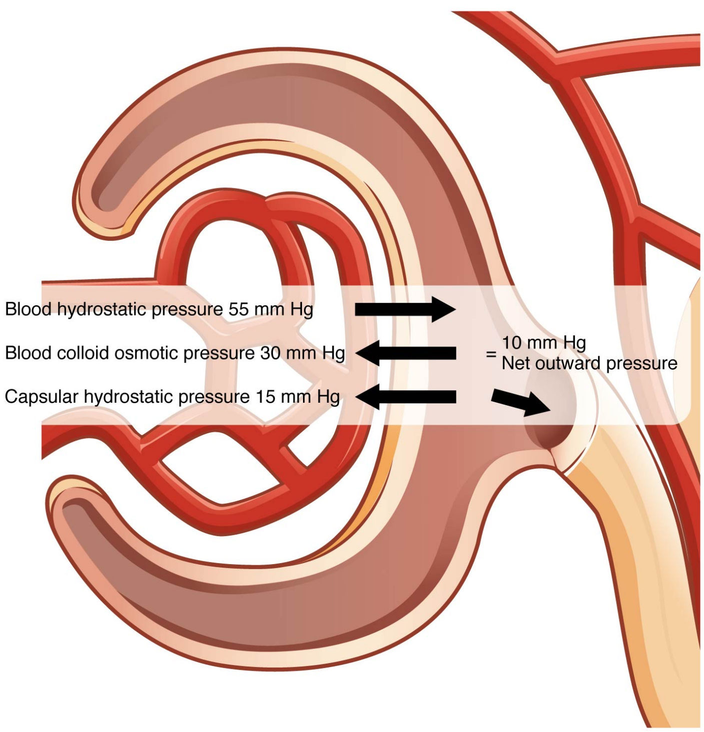
Calculating Urine Formation per Day		
	Flow per minute (mL)	**Calculation**
Renal blood flow	1050	Cardiac output is about 5000 mL/minute, of which 21 percent flows through the kidney. 5000*0.21 = 1050 mL blood/min
Renal plasma flow	578	Renal plasma flow equals the blood flow per minute times the hematocrit. If a person has a hematocrit of 45, then the renal plasma flow is 55 percent. 1050*0.55 = 578 mL plasma/min
Glomerular filtration rate	110	The GFR is the amount of plasma entering Bowman's capsule per minute. It is the renal plasma flow times the fraction that enters the renal capsule (19 percent). 578*0.19 = 110 mL filtrate/min

Calculating Urine Formation per Day		
	Flow per minute (mL)	**Calculation**
Urine	1296 ml/day	The filtrate not recovered by the kidney is the urine that will be eliminated. It is the GFR times the fraction of the filtrate that is not reabsorbed (0.8 percent). 110*.008 = 0.9 mL urine /min Multiply urine/min times 60 minutes times 24 hours to get daily urine production. 0.9*60*24 = 1296 mL/day urine

GFR is influenced by the hydrostatic pressure and colloid osmotic pressure on either side of the capillary membrane of the glomerulus. Recall that filtration occurs as pressure forces fluid and solutes through a semipermeable barrier with the solute movement constrained by particle size. Hydrostatic pressure is the pressure produced by a fluid against a surface. If you have a fluid on both sides of a barrier, both fluids exert a pressure in opposing directions. Net fluid movement will be in the direction of the lower pressure. Osmosis is the movement of solvent (water) across a membrane that is impermeable to a solute in the solution. This creates a pressure, osmotic pressure, which will exist until the solute concentration is the same on both sides of a semipermeable membrane. As long as the concentration differs, water will move. Glomerular filtration occurs when glomerular hydrostatic pressure exceeds the luminal hydrostatic pressure of Bowman’s capsule. There is also an opposing force, the osmotic pressure, which is typically higher in the glomerular capillary.

To understand why this is so, look more closely at the microenvironment on either side of the filtration membrane. You will find osmotic pressure exerted by the solutes inside the lumen of the capillary as well as inside of Bowman's capsule. Since the filtration membrane limits the size of particles crossing the membrane, the osmotic pressure inside the glomerular capillary is higher than the osmotic pressure in Bowman's capsule. Recall that cells and the medium-to-large proteins cannot pass between the podocyte processes or through the fenestrations of the capillary endothelial cells. This means that red and white blood cells, platelets, albumins, and other proteins too large to pass through the filter remain in the capillary, creating an average colloid osmotic pressure of 30 mm Hg within the capillary. The absence of proteins in Bowman's space (the lumen within Bowman's capsule) results in an osmotic pressure near zero. Thus, the only pressure moving fluid across the capillary wall into the lumen of Bowman's space is hydrostatic pressure. Hydrostatic (fluid) pressure is sufficient to push water through the membrane despite the osmotic pressure working against it. The sum of all of the influences, both osmotic and hydrostatic, results in a **net filtration pressure (NFP)** of about 10 mm Hg ([link]).

Net Filtration Pressure



The NFP is the sum of osmotic and

hydrostatic pressures.

A proper concentration of solutes in the blood is important in maintaining osmotic pressure both in the glomerulus and systemically. There are disorders in which too much protein passes through the filtration slits into the kidney filtrate. This excess protein in the filtrate leads to a deficiency of circulating plasma proteins. In turn, the presence of protein in the urine increases its osmolarity; this holds more water in the filtrate and results in an increase in urine volume. Because there is less circulating protein, principally albumin, the osmotic pressure of the blood falls. Less osmotic pressure pulling water into the capillaries tips the balance towards hydrostatic pressure, which tends to push it out of the capillaries. The net effect is that water is lost from the circulation to interstitial tissues and cells. This “plumps up” the tissues and cells, a condition termed **systemic edema**.

Net Filtration Pressure (NFP)

NFP determines filtration rates through the kidney. It is determined as follows:

NFP = Glomerular blood hydrostatic pressure (GBHP) – [capsular hydrostatic pressure (CHP) + blood colloid osmotic pressure (BCOP)] = 10 mm Hg

That is:

NFP = GBHP – [CHP + BCOP] = 10 mm Hg

Or:

NFP = 55 – [15 + 30] = 10 mm Hg

As you can see, there is a low net pressure across the filtration membrane. Intuitively, you should realize that minor changes in osmolarity of the blood or changes in capillary blood pressure result in major changes in the amount

of filtrate formed at any given point in time. The kidney is able to cope with a wide range of blood pressures. In large part, this is due to the autoregulatory nature of smooth muscle. When you stretch it, it contracts. Thus, when blood pressure goes up, smooth muscle in the afferent capillaries contracts to limit any increase in blood flow and filtration rate. When blood pressure drops, the same capillaries relax to maintain blood flow and filtration rate. The net result is a relatively steady flow of blood into the glomerulus and a relatively steady filtration rate in spite of significant systemic blood pressure changes. Mean arterial blood pressure is calculated by adding 1/3 of the difference between the systolic and diastolic pressures to the diastolic pressure. Therefore, if the blood pressure is 110/80, the difference between systolic and diastolic pressure is 30. One third of this is 10, and when you add this to the diastolic pressure of 80, you arrive at a calculated mean arterial pressure of 90 mm Hg. Therefore, if you use mean arterial pressure for the GBHP in the formula for calculating NFP, you can determine that as long as mean arterial pressure is above approximately 60 mm Hg, the pressure will be adequate to maintain glomerular filtration. Blood pressures below this level will impair renal function and cause systemic disorders that are severe enough to threaten survival. This condition is called shock.

Determination of the GFR is one of the tools used to assess the kidney's excretory function. This is more than just an academic exercise. Since many drugs are excreted in the urine, a decline in renal function can lead to toxic accumulations. Additionally, administration of appropriate drug dosages for those drugs primarily excreted by the kidney requires an accurate assessment of GFR. GFR can be estimated closely by intravenous administration of **inulin**. Inulin is a plant polysaccharide that is neither reabsorbed nor secreted by the kidney. Its appearance in the urine is directly proportional to the rate at which it is filtered by the renal corpuscle. However, since measuring inulin clearance is cumbersome in the clinical setting, most often, the GFR is estimated by measuring naturally occurring creatinine, a protein-derived molecule produced by muscle metabolism that is not reabsorbed and only slightly secreted by the nephron.

Chapter Review

The entire volume of the blood is filtered through the kidneys about 300 times per day, and 99 percent of the water filtered is recovered. The GFR is influenced by hydrostatic pressure and colloid osmotic pressure. Under normal circumstances, hydrostatic pressure is significantly greater and filtration occurs. The hydrostatic pressure of the glomerulus depends on systemic blood pressure, autoregulatory mechanisms, sympathetic nervous activity, and paracrine hormones. The kidney can function normally under a wide range of blood pressures due to the autoregulatory nature of smooth muscle.

Review Questions

Exercise:

Problem:

_________ pressure must be greater on the capillary side of the filtration membrane to achieve filtration.

a. Osmotic
b. Hydrostatic

Solution:

B

Exercise:

Problem:

Production of urine to modify plasma makeup is the result of _________.

a. filtration
b. absorption
c. secretion
d. filtration, absorption, and secretion

Solution:

D

Exercise:

Problem:

Systemic blood pressure must stay above 60 so that the proper amount of filtration occurs.

a. true
b. false

Solution:

B

Critical Thinking Questions

Exercise:

Problem: Give the formula for net filtration pressure.

Solution:

Net filtration pressure (NFP) = glomerular blood hydrostatic pressure (GBHP) – [capsular hydrostatic pressure (CHP) + blood colloid osmotic pressure (BCOP)]

Exercise:

Problem: Name at least five symptoms of kidney failure.

Solution:

Symptoms of kidney failure are weakness, lethargy, shortness of breath, widespread edema, anemia, metabolic acidosis or alkalosis, heart arrhythmias, uremia, loss of appetite, fatigue, excessive urination, and oliguria.

Glossary

glomerular filtration rate (GFR)
: rate of renal filtration

inulin
: plant polysaccharide injected to determine GFR; is neither secreted nor absorbed by the kidney, so its appearance in the urine is directly proportional to its filtration rate

net filtration pressure (NFP)
: pressure of fluid across the glomerulus; calculated by taking the hydrostatic pressure of the capillary and subtracting the colloid osmotic pressure of the blood and the hydrostatic pressure of Bowman’s capsule

systemic edema
: increased fluid retention in the interstitial spaces and cells of the body; can be seen as swelling over large areas of the body, particularly the lower extremities

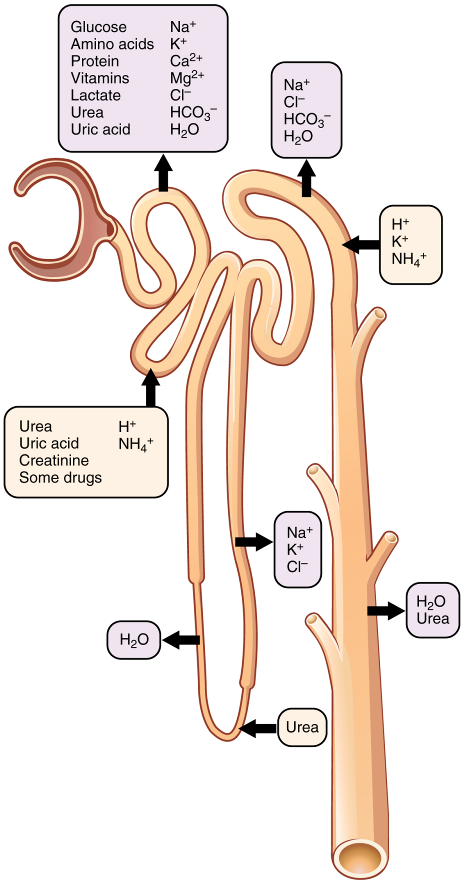
Tubular Reabsorption

By the end of this section, you will be able to:

- List specific transport mechanisms occurring in different parts of the nephron, including active transport, osmosis, facilitated diffusion, and passive electrochemical gradients
- List the different membrane proteins of the nephron, including channels, transporters, and ATPase pumps
- Compare and contrast passive and active tubular reabsorption
- Explain why the differential permeability or impermeability of specific sections of the nephron tubules is necessary for urine formation
- Describe how and where water, organic compounds, and ions are reabsorbed in the nephron
- Explain the role of the loop of Henle, the vasa recta, and the countercurrent multiplication mechanisms in the concentration of urine
- List the locations in the nephron where tubular secretion occurs

With up to 180 liters per day passing through the nephrons of the kidney, it is quite obvious that most of that fluid and its contents must be reabsorbed. That recovery occurs in the PCT, loop of Henle, DCT, and the collecting ducts ([link] and [link]). Various portions of the nephron differ in their capacity to reabsorb water and specific solutes. While much of the reabsorption and secretion occur passively based on concentration gradients, the amount of water that is reabsorbed or lost is tightly regulated. This control is exerted directly by ADH and aldosterone, and indirectly by renin. Most water is recovered in the PCT, loop of Henle, and DCT. About 10 percent (about 18 L) reaches the collecting ducts. The collecting ducts, under the influence of ADH, can recover almost all of the water passing through them, in cases of dehydration, or almost none of the water, in cases of over-hydration.

Locations of Secretion and Reabsorption in the Nephron



Substances Secreted or Reabsorbed in the Nephron and Their Locations				
Substance	**PCT**	**Loop of Henle**	**DCT**	**Collecting ducts**
Glucose	Almost 100 percent reabsorbed; secondary active transport with Na^+			

Substances Secreted or Reabsorbed in the Nephron and Their Locations				
Substance	**PCT**	**Loop of Henle**	**DCT**	**Collecting ducts**
Oligopeptides, proteins, amino acids	Almost 100 percent reabsorbed; symport with Na^+			
Vitamins	Reabsorbed			
Lactate	Reabsorbed			
Creatinine	Secreted			
Urea	50 percent reabsorbed by diffusion; also secreted	Secretion, diffusion in descending limb		Reabsorption in medullary collecting ducts; diffusion
Sodium	65 percent actively reabsorbed	25 percent reabsorbed in thick ascending limb; active transport	5 percent reabsorbed; active	5 percent reabsorbed, stimulated by aldosterone; active
Chloride	Reabsorbed, symport with Na^+, diffusion	Reabsorbed in thin and thick ascending limb; diffusion in ascending limb	Reabsorbed; diffusion	Reabsorbed; symport

Substances Secreted or Reabsorbed in the Nephron and Their Locations				
Substance	**PCT**	**Loop of Henle**	**DCT**	**Collecting ducts**
Water	67 percent reabsorbed osmotically with solutes	15 percent reabsorbed in descending limb; osmosis	8 percent reabsorbed if ADH; osmosis	Variable amounts reabsorbed, controlled by ADH, osmosis
Bicarbonate	80–90 percent symport reabsorption with Na^+	Reabsorbed, symport with Na^+ and antiport with Cl^-; in ascending limb		Reabsorbed antiport with Cl^-
H^+	Secreted; diffusion		Secreted; active	Secreted; active
NH_4^+	Secreted; diffusion		Secreted; diffusion	Secreted; diffusion
HCO_3^-	Reabsorbed; diffusion	Reabsorbed; diffusion in ascending limb	Reabsorbed; diffusion	Reabsorbed; antiport with Na^+
Some drugs	Secreted		Secreted; active	Secreted; active
Potassium	65 percent reabsorbed; diffusion	20 percent reabsorbed in thick ascending limb; symport	Secreted; active	Secretion controlled by aldosterone; active

Substances Secreted or Reabsorbed in the Nephron and Their Locations				
Substance	**PCT**	**Loop of Henle**	**DCT**	**Collecting ducts**
Calcium	Reabsorbed; diffusion	Reabsorbed in thick ascending limb; diffusion		Reabsorbed if parathyroid hormone present; active
Magnesium	Reabsorbed; diffusion	Reabsorbed in thick ascending limb; diffusion	Reabsorbed	
Phosphate	85 percent reabsorbed, inhibited by parathyroid hormone, diffusion		Reabsorbed; diffusion	

Mechanisms of Recovery

Mechanisms by which substances move across membranes for reabsorption or secretion include active transport, diffusion, facilitated diffusion, secondary active transport, and osmosis. These were discussed in an earlier chapter, and you may wish to review them.

Active transport utilizes energy, usually the energy found in a phosphate bond of ATP, to move a substance across a membrane from a low to a high concentration. It is very specific and must have an appropriately shaped receptor for the substance to be transported. An example would be the active transport of Na^+ out of a cell and K^+ into a cell by the Na^+/K^+ pump. Both ions are moved in opposite directions from a lower to a higher concentration.

Simple diffusion moves a substance from a higher to a lower concentration down its concentration gradient. It requires no energy and only needs to be soluble.

Facilitated diffusion is similar to diffusion in that it moves a substance down its concentration gradient. The difference is that it requires specific membrane receptors or channel proteins for movement. The movement of glucose and, in certain situations, Na^+ ions, is an example of facilitated diffusion. In some cases of mediated transport, two

different substances share the same channel protein port; these mechanisms are described by the terms symport and antiport.

Symport mechanisms move two or more substances in the same direction at the same time, whereas antiport mechanisms move two or more substances in opposite directions across the cell membrane. Both mechanisms may utilize concentration gradients maintained by ATP pumps. As described previously, when active transport powers the transport of another substance in this way, it is called “secondary active transport.” Glucose reabsorption in the kidneys is by secondary active transport. Na^+/K^+ ATPases on the basal membrane of a tubular cell constantly pump Na^+ out of the cell, maintaining a strong electrochemical gradient for Na^+ to move into the cell from the tubular lumen. On the luminal (apical) surface, a Na^+/glucose symport protein assists both Na+ and glucose movement into the cell. The cotransporter moves glucose into the cell against its concentration gradient as Na^+ moves down the electrochemical gradient created by the basal membranes Na^+/K^+ ATPases. The glucose molecule then diffuses across the basal membrane by facilitated diffusion into the interstitial space and from there into peritubular capillaries.

Most of the Ca^{++}, Na^+, glucose, and amino acids must be reabsorbed by the nephron to maintain homeostatic plasma concentrations. Other substances, such as urea, K^+, ammonia ($NH_{3)}$, creatinine, and some drugs are secreted into the filtrate as waste products. Acid–base balance is maintained through actions of the lungs and kidneys: The lungs rid the body of H^+, whereas the kidneys secrete or reabsorb H^+ and HCO_3^- ([link]). In the case of urea, about 50 percent is passively reabsorbed by the PCT. More is recovered by in the collecting ducts as needed. ADH induces the insertion of urea transporters and aquaporin channel proteins.

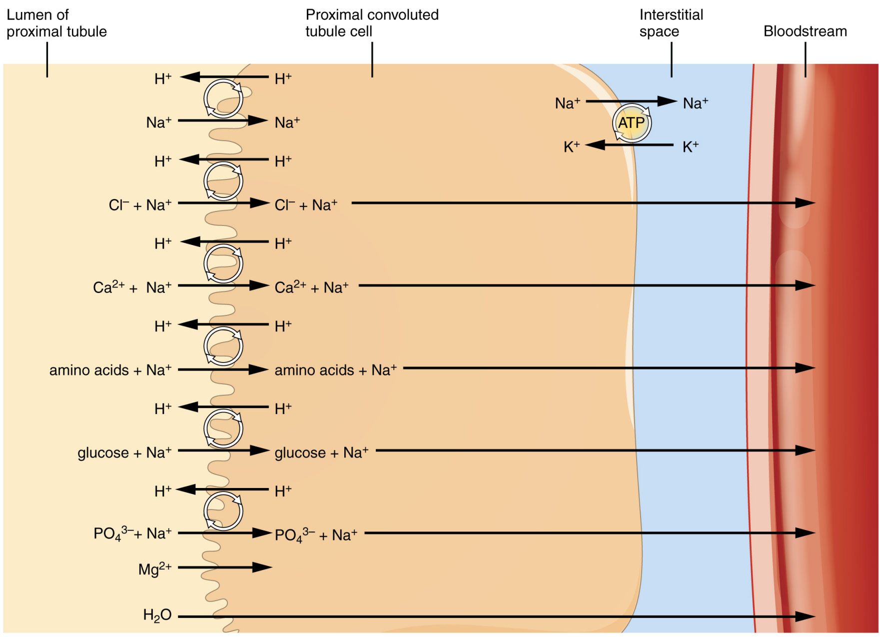
Substances Filtered and Reabsorbed by the Kidney per 24 Hours			
Substance	**Amount filtered (grams)**	**Amount reabsorbed (grams)**	**Amount in urine (grams)**
Water	180 L	179 L	1 L
Proteins	10–20	10–20	0
Chlorine	630	625	5
Sodium	540	537	3
Bicarbonate	300	299.7	0.3

Substances Filtered and Reabsorbed by the Kidney per 24 Hours			
Substance	**Amount filtered (grams)**	**Amount reabsorbed (grams)**	**Amount in urine (grams)**
Glucose	180	180	0
Urea	53	28	25
Potassium	28	24	4
Uric acid	8.5	7.7	0.8
Creatinine	1.4	0	1.4

Reabsorption and Secretion in the PCT

The renal corpuscle filters the blood to create a filtrate that differs from blood mainly in the absence of cells and large proteins. From this point to the ends of the collecting ducts, the filtrate or forming urine is undergoing modification through secretion and reabsorption before true urine is produced. The first point at which the forming urine is modified is in the PCT. Here, some substances are reabsorbed, whereas others are secreted. Note the use of the term "reabsorbed." All of these substances were "absorbed" in the digestive tract—99 percent of the water and most of the solutes filtered by the nephron must be reabsorbed. Water and substances that are reabsorbed are returned to the circulation by the peritubular and vasa recta capillaries. It is important to understand the difference between the glomerulus and the peritubular and vasa recta capillaries. The glomerulus has a relatively high pressure inside its capillaries and can sustain this by dilating the afferent arteriole while constricting the efferent arteriole. This assures adequate filtration pressure even as the systemic blood pressure varies. Movement of water into the peritubular capillaries and vasa recta will be influenced primarily by osmolarity and concentration gradients. Sodium is actively pumped out of the PCT into the interstitial spaces between cells and diffuses down its concentration gradient into the peritubular capillary. As it does so, water will follow passively to maintain an isotonic fluid environment inside the capillary. This is called obligatory water reabsorption, because water is "obliged" to follow the Na^+ ([link]).

Substances Reabsorbed and Secreted by the PCT



More substances move across the membranes of the PCT than any other portion of the nephron. Many of these substances (amino acids and glucose) use symport mechanisms for transport along with Na^+. Antiport, active transport, diffusion, and facilitated diffusion are additional mechanisms by which substances are moved from one side of a membrane to the other. Recall that cells have two surfaces: apical and basal. The apical surface is the one facing the lumen or open space of a cavity or tube, in this case, the inside of the PCT. The basal surface of the cell faces the connective tissue base to which the cell attaches (basement membrane) or the cell membrane closer to the basement membrane if there is a stratified layer of cells. In the PCT, there is a single layer of simple cuboidal endothelial cells against the basement membrane. The numbers and particular types of pumps and channels vary between the apical and basilar surfaces. A few of the substances that are transported with Na^+ (symport mechanism) on the apical membrane include $Cl^–$, Ca^{++}, amino acids, glucose, and PO_4^{3-}. Sodium is actively exchanged for K^+ using ATP on the basal membrane. Most of the substances transported by a symport mechanism on the apical membrane are transported by facilitated diffusion on the basal membrane. At least three ions, K^+, Ca^{++}, and Mg^{++}, diffuse laterally between adjacent cell membranes (transcellular).

About 67 percent of the water, Na^+, and K^+ entering the nephron is reabsorbed in the PCT and returned to the circulation. Almost 100 percent of glucose, amino acids, and other organic substances such as vitamins are normally recovered here. Some glucose may appear in the urine if circulating glucose levels are high enough that all the glucose transporters in the PCT are saturated, so that their capacity to move glucose is exceeded (transport maximum, or T_m). In men, the maximum amount of glucose that can be recovered is about 375 mg/min, whereas in women, it is about 300 mg/min. This recovery rate translates to an arterial concentration of about 200 mg/dL. Though an exceptionally high sugar intake might cause sugar to appear briefly in the urine, the appearance of **glycosuria** usually points to type I or II diabetes mellitus. The transport of glucose from the lumen of the PCT

to the interstitial space is similar to the way it is absorbed by the small intestine. Both glucose and Na^+ bind simultaneously to the same symport proteins on the apical surface of the cell to be transported in the same direction, toward the interstitial space. Sodium moves down its electrochemical and concentration gradient into the cell and takes glucose with it. Na^+ is then actively pumped out of the cell at the basal surface of the cell into the interstitial space. Glucose leaves the cell to enter the interstitial space by facilitated diffusion. The energy to move glucose comes from the Na^+/K^+ ATPase that pumps Na^+ out of the cell on the basal surface. Fifty percent of Cl^- and variable quantities of Ca^{++}, Mg^{++}, and HPO_4^{2-} are also recovered in the PCT.

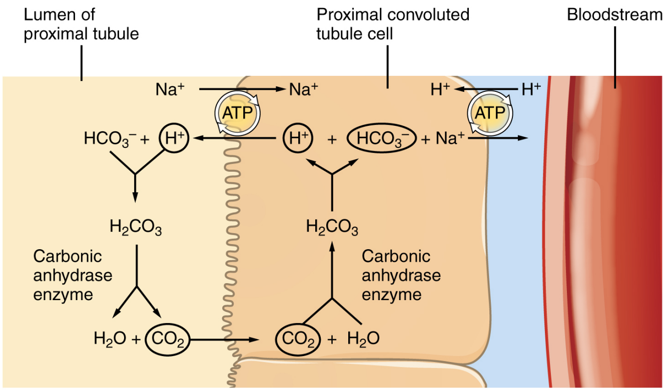
Recovery of bicarbonate (HCO_3^-) is vital to the maintenance of acid–base balance, since it is a very powerful and fast-acting buffer. An important enzyme is used to catalyze this mechanism: carbonic anhydrase (CA). This same enzyme and reaction is used in red blood cells in the transportation of CO_2, in the stomach to produce hydrochloric acid, and in the pancreas to produce HCO_3^- to buffer acidic chyme from the stomach. In the kidney, most of the CA is located within the cell, but a small amount is bound to the brush border of the membrane on the apical surface of the cell. In the lumen of the PCT, HCO_3^- combines with hydrogen ions to form carbonic acid (H_2CO_3). This is enzymatically catalyzed into CO_2 and water, which diffuse across the apical membrane into the cell. Water can move osmotically across the lipid bilayer membrane due to the presence of aquaporin water channels. Inside the cell, the reverse reaction occurs to produce bicarbonate ions (HCO_3^-). These bicarbonate ions are cotransported with Na^+ across the basal membrane to the interstitial space around the PCT ([link]). At the same time this is occurring, a Na^+/H^+ antiporter excretes H^+ into the lumen, while it recovers Na^+. Note how the hydrogen ion is recycled so that bicarbonate can be recovered. Also, note that a Na^+ gradient is created by the Na^+/K^+ pump.

Equation:

$$\mathrm{HCO_{3-} + H^+ \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O}$$

The significant recovery of solutes from the PCT lumen to the interstitial space creates an osmotic gradient that promotes water recovery. As noted before, water moves through channels created by the aquaporin proteins. These proteins are found in all cells in varying amounts and help regulate water movement across membranes and through cells by creating a passageway across the hydrophobic lipid bilayer membrane. Changing the number of aquaporin proteins in membranes of the collecting ducts also helps to regulate the osmolarity of the blood. The movement of many positively charged ions also creates an electrochemical gradient. This charge promotes the movement of negative ions toward the interstitial spaces and the movement of positive ions toward the lumen.

Reabsorption of Bicarbonate from the PCT



Reabsorption and Secretion in the Loop of Henle

The loop of Henle consists of two sections: thick and thin descending and thin and thick ascending sections. The loops of cortical nephrons do not extend into the renal medulla very far, if at all. Juxtamedullary nephrons have loops that extend variable distances, some very deep into the medulla. The descending and ascending portions of the loop are highly specialized to enable recovery of much of the Na^+ and water that were filtered by the glomerulus. As the forming urine moves through the loop, the osmolarity will change from isosmotic with blood (about 278–300 mOsmol/kg) to both a very hypertonic solution of about 1200 mOsmol/kg and a very hypotonic solution of about 100 mOsmol/kg. These changes are accomplished by osmosis in the descending limb and active transport in the ascending limb. Solutes and water recovered from these loops are returned to the circulation by way of the vasa recta.

Descending Loop

The majority of the descending loop is comprised of simple squamous epithelial cells; to simplify the function of the loop, this discussion focuses on these cells. These membranes have permanent aquaporin channel proteins that allow unrestricted movement of water from the descending loop into the surrounding interstitium as osmolarity increases from about 300 mOsmol/kg to about 1200 mOsmol/kg. This increase results in reabsorption of up to 15 percent of the water entering the nephron. Modest amounts of urea, Na^+, and other ions are also recovered here.

Most of the solutes that were filtered in the glomerulus have now been recovered along with a majority of water, about 82 percent. As the forming urine enters the ascending loop, major adjustments will be made to the concentration of solutes to create what you perceive as urine.

Ascending Loop

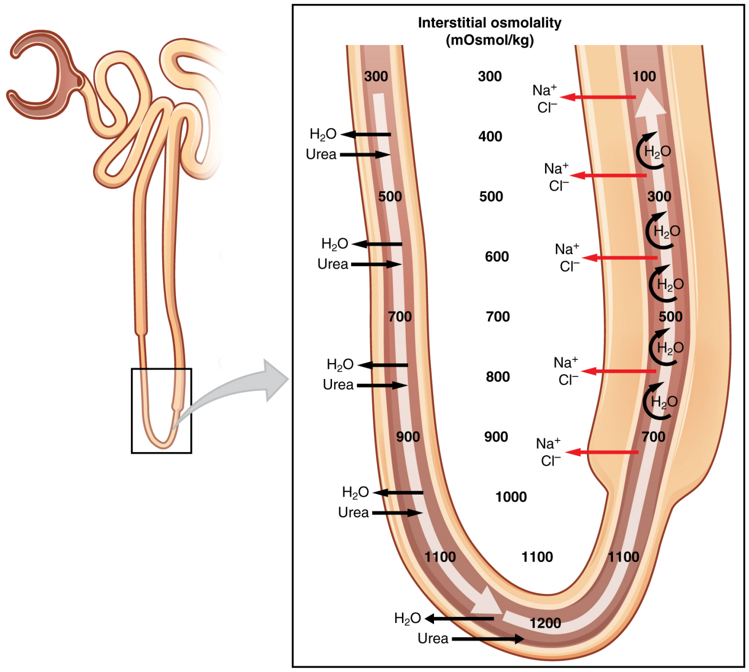
The ascending loop is made of very short thin and longer thick portions. Once again, to simplify the function, this section only considers the thick portion. The thick portion is lined with simple cuboidal epithelium without a brush border. It is completely impermeable to water due to the absence of aquaporin proteins, but ions, mainly Na^+ and $CL^–$, are actively reabsorbed by a cotransport system. This has two significant effects: Removal of NaCl while retaining water leads to a hypoosomotic filtrate by the time it reaches the DCT; pumping NaCl into the interstitial space contributes to the hyperosmotic environment in the kidney medulla.

The $Na^{+/}K^+$ ATPase pumps in the basal membrane create an electrochemical gradient, allowing reabsorption of $Cl^–$ by $Na^+/Cl^–$ symporters in the apical membrane. At the same time that Na^+ is actively pumped from the basal side of the cell into the interstitial fluid, $Cl^–$ follows the Na^+ from the lumen into the interstitial fluid by a paracellular route between cells through **leaky tight junctions**. These are found between cells of the ascending loop, where they allow certain solutes to move according to their concentration gradient. Most of the K^+ that enters the cell via symporters returns to the lumen (down its concentration gradient) through leaky channels in the apical membrane. Note the environment now created in the interstitial space: With the “back door exiting” K^+, there is one Na^+ and two $Cl^–$ ions left in the interstitium surrounding the ascending loop. Therefore, in comparison to the lumen of the loop, the interstitial space is now a negatively charged environment. This negative charge attracts cations (Na^+, K^+, Ca^{++}, and Mg^{++}) from the lumen via a paracellular route to the interstitial space and vasa recta.

Countercurrent Multiplier System

The structure of the loop of Henle and associated vasa recta create a **countercurrent multiplier system** ([link]). The countercurrent term comes from the fact that the descending and ascending loops are next to each other and their fluid flows in opposite directions (countercurrent). The multiplier term is due to the action of solute pumps that increase (multiply) the concentrations of urea and Na^+ deep in the medulla.

Countercurrent Multiplier System



As discussed above, the ascending loop actively reabsorbs NaCl out of the forming urine into the interstitial spaces. In addition, collecting ducts have urea pumps that actively pump urea into the interstitial spaces. This results in the recovery of NaCl to the circulation via the vasa recta and creates a high osmolar environment in the depths of the medulla.

Ammonia (NH_3) is a toxic byproduct of protein metabolism. It is formed as amino acids are deaminated by liver hepatocytes. That means that the amine group, NH_2, is removed from amino acids as they are broken down. Most of the resulting ammonia is converted into urea by liver hepatocytes. Urea is not only less toxic but is utilized to aid in the recovery of water by the loop of Henle and collecting ducts. At the same time that water is freely diffusing out of the descending loop through aquaporin channels into the interstitial spaces of the medulla, urea freely diffuses into the lumen of the descending loop as it descends deeper into the medulla, much of it to be reabsorbed from the forming urine when it reaches the collecting duct. Thus, the movement of Na^+ and urea into the interstitial spaces by these mechanisms creates the hyperosmotic environment of the medulla. The net result of this countercurrent multiplier system is to recover both water and Na^+ in the circulation.

The amino acid glutamine can be deaminated by the kidney. As NH_2 from the amino acid is converted into NH_3 and pumped into the lumen of the PCT, Na^+ and HCO_3^- are excreted into the interstitial fluid of the renal pyramid via a symport mechanism. When this process occurs in the cells of the PCT, the added benefit is a net loss of a hydrogen ion (complexed to ammonia to form the weak acid NH_4^+) in the urine and a gain of a bicarbonate ion (HCO_3^-) in the blood. Ammonia and bicarbonate are exchanged in a one-to-one ratio. This exchange is yet another means by which the body can buffer and excrete acid. The presence of aquaporin channels in the descending loop allows prodigious quantities of water to leave the loop and enter the hyperosmolar interstitium of the pyramid, where it is returned to the

circulation by the vasa recta. As the loop turns to become the ascending loop, there is an absence of aquaporin channels, so water cannot leave the loop. However, in the basal membrane of cells of the thick ascending loop, ATPase pumps actively remove Na^+ from the cell. A $Na^+/K^+/2Cl^-$ symporter in the apical membrane passively allows these ions to enter the cell cytoplasm from the lumen of the loop down a concentration gradient created by the pump. This mechanism works to dilute the fluid of the ascending loop ultimately to approximately 50–100 mOsmol/L.

At the transition from the DCT to the collecting duct, about 20 percent of the original water is still present and about 10 percent of the sodium. If no other mechanism for water reabsorption existed, about 20–25 liters of urine would be produced. Now consider what is happening in the adjacent capillaries, the vasa recta. They are recovering both solutes and water at a rate that preserves the countercurrent multiplier system. In general, blood flows slowly in capillaries to allow time for exchange of nutrients and wastes. In the vasa recta particularly, this rate of flow is important for two additional reasons. The flow must be slow to allow blood cells to lose and regain water without either crenating or bursting. Second, a rapid flow would remove too much Na^+ and urea, destroying the osmolar gradient that is necessary for the recovery of solutes and water. Thus, by flowing slowly to preserve the countercurrent mechanism, as the vasa recta descend, Na^+ and urea are freely able to enter the capillary, while water freely leaves; as they ascend, Na^+ and urea are secreted into the surrounding medulla, while water reenters and is removed.

Note:

Watch this video to learn about the countercurrent multiplier system.

Reabsorption and Secretion in the Distal Convoluted Tubule

Approximately 80 percent of filtered water has been recovered by the time the dilute forming urine enters the DCT. The DCT will recover another 10–15 percent before the forming urine enters the collecting ducts. Aldosterone increases the amount of Na^+/K^+ ATPase in the basal membrane of the DCT and collecting duct. The movement of Na^+ out of the lumen of the collecting duct creates a negative charge that promotes the movement of Cl^- out of the lumen into the interstitial space by a paracellular route across tight junctions. Peritubular capillaries receive the solutes and water, returning them to the circulation.

Cells of the DCT also recover Ca^{++} from the filtrate. Receptors for parathyroid hormone (PTH) are found in DCT cells and when bound to PTH, induce the insertion of calcium channels on their luminal surface. The channels enhance Ca^{++} recovery from the forming urine. In addition, as Na^{+} is pumped out of the cell, the resulting electrochemical gradient attracts Ca^{++} into the cell. Finally, calcitriol (1,25 dihydroxyvitamin D, the active form of vitamin D) is very important for calcium recovery. It induces the production of calcium-binding proteins that transport Ca^{++} into the cell. These binding proteins are also important for the movement of calcium inside the cell and aid in exocytosis of calcium across the basolateral membrane. Any Ca^{++} not reabsorbed at this point is lost in the urine.

Collecting Ducts and Recovery of Water

Solutes move across the membranes of the collecting ducts, which contain two distinct cell types, principal cells and intercalated cells. A **principal cell** possesses channels for the recovery or loss of sodium and potassium. An **intercalated cell** secretes or absorbs acid or bicarbonate. As in other portions of the nephron, there is an array of micromachines (pumps and channels) on display in the membranes of these cells.

Regulation of urine volume and osmolarity are major functions of the collecting ducts. By varying the amount of water that is recovered, the collecting ducts play a major role in maintaining the body’s normal osmolarity. If the blood becomes hyperosmotic, the collecting ducts recover more water to dilute the blood; if the blood becomes hyposmotic, the collecting ducts recover less of the water, leading to concentration of the blood. Another way of saying this is: If plasma osmolarity rises, more water is recovered and urine volume decreases; if plasma osmolarity decreases, less water is recovered and urine volume increases. This function is regulated by the posterior pituitary hormone ADH (vasopressin). With mild dehydration, plasma osmolarity rises slightly. This increase is detected by osmoreceptors in the hypothalamus, which stimulates the release of ADH from the posterior pituitary. If plasma osmolarity decreases slightly, the opposite occurs.

When stimulated by ADH, aquaporin channels are inserted into the apical membrane of principal cells, which line the collecting ducts. As the ducts descend through the medulla, the osmolarity surrounding them increases (due to the countercurrent mechanisms described above). If aquaporin water channels are present, water will be osmotically pulled from the collecting duct into the surrounding interstitial space and into the peritubular capillaries. Therefore, the final urine will be more concentrated. If less ADH is secreted, fewer aquaporin channels are inserted and less water is recovered, resulting in dilute urine. By altering the number of aquaporin channels, the volume of water recovered or lost is altered. This, in turn, regulates the blood osmolarity, blood pressure, and osmolarity of the urine.

As Na^{+} is pumped from the forming urine, water is passively recaptured for the circulation; this preservation of vascular volume is critically important for the maintenance of a normal blood pressure. Aldosterone is secreted by the adrenal cortex in response to angiotensin II stimulation. As an extremely potent vasoconstrictor, angiotensin II functions immediately

to increase blood pressure. By also stimulating aldosterone production, it provides a longer-lasting mechanism to support blood pressure by maintaining vascular volume (water recovery).

In addition to receptors for ADH, principal cells have receptors for the steroid hormone aldosterone. While ADH is primarily involved in the regulation of water recovery, aldosterone regulates Na^+ recovery. Aldosterone stimulates principal cells to manufacture luminal Na^+ and K^+ channels as well as Na^+/K^+ ATPase pumps on the basal membrane of the cells. When aldosterone output increases, more Na^+ is recovered from the forming urine and water follows the Na^+ passively. As the pump recovers Na^+ for the body, it is also pumping K^+ into the forming urine, since the pump moves K^+ in the opposite direction. When aldosterone decreases, more Na^+ remains in the forming urine and more K^+ is recovered in the circulation. Symport channels move Na^+ and $Cl^–$ together. Still other channels in the principal cells secrete K^+ into the collecting duct in direct proportion to the recovery of Na^+.

Intercalated cells play significant roles in regulating blood pH. Intercalated cells reabsorb K^+ and $HCO_3^–$ while secreting H^+. This function lowers the acidity of the plasma while increasing the acidity of the urine.

Chapter Review

The kidney regulates water recovery and blood pressure by producing the enzyme renin. It is renin that starts a series of reactions, leading to the production of the vasoconstrictor angiotensin II and the salt-retaining steroid aldosterone. Water recovery is also powerfully and directly influenced by the hormone ADH. Even so, it only influences the last 10 percent of water available for recovery after filtration at the glomerulus, because 90 percent of water is recovered before reaching the collecting ducts. Depending on the body’s fluid status at any given time, the collecting ducts can recover none or almost all of the water reaching them.

Mechanisms of solute recovery include active transport, simple diffusion, and facilitated diffusion. Most filtered substances are reabsorbed. Urea, NH_3, creatinine, and some drugs are filtered or secreted as wastes. H^+ and $HCO_3^–$ are secreted or reabsorbed as needed to maintain acid–base balance. Movement of water from the glomerulus is primarily due to pressure, whereas that of peritubular capillaries and vasa recta is due to osmolarity and concentration gradients. The PCT is the most metabolically active part of the nephron and uses a wide array of protein micromachines to maintain homeostasis—symporters, antiporters, and ATPase active transporters—in conjunction with diffusion, both simple and facilitated. Almost 100 percent of glucose, amino acids, and vitamins are recovered in the PCT. Bicarbonate ($HCO_3^–$) is recovered using the same enzyme, carbonic anhydrase (CA), found in erythrocytes. The recovery of solutes creates an osmotic gradient to promote the recovery of water. The descending loop of the juxtaglomerular nephrons reaches an osmolarity of up to 1200 mOsmol/kg, promoting the recovery of water. The ascending loop is impervious to water but actively recovers Na^+, reducing filtrate osmolarity to 50–100

mOsmol/kg. The descending and ascending loop and vasa recta form a countercurrent multiplier system to increase Na^+ concentration in the kidney medulla. The collecting ducts actively pump urea into the medulla, further contributing to the high osmotic environment. The vasa recta recover the solute and water in the medulla, returning them to the circulation. Nearly 90 percent of water is recovered before the forming urine reaches the DCT, which will recover another 10 percent. Calcium recovery in the DCT is influenced by PTH and active vitamin D. In the collecting ducts, ADH stimulates aquaporin channel insertion to increase water recovery and thereby regulate osmolarity of the blood. Aldosterone stimulates Na^+ recovery by the collecting duct.

Review Questions

Exercise:

Problem: Aquaporin channels are only found in the collecting duct.

a. true
b. false

Solution:

B

Exercise:

Problem: Most absorption and secretion occurs in this part of the nephron.

a. proximal convoluted tubule
b. descending loop of Henle
c. ascending loop of Henle
d. distal convoluted tubule
e. collecting ducts

Solution:

A

Exercise:

Problem: The fine tuning of water recovery or disposal occurs in _________.

a. the proximal convoluted tubule
b. the collecting ducts

c. the ascending loop of Henle
d. the distal convoluted tubule

Solution:

B

Critical Thinking Questions

Exercise:

Problem:

Which vessels and what part of the nephron are involved in countercurrent multiplication?

Solution:

The vasa recta and loop of Henle are involved in countercurrent multiplication.

Exercise:

Problem:

Give the approximate osmolarity of fluid in the proximal convoluted tubule, deepest part of the loop of Henle, distal convoluted tubule, and the collecting ducts.

Solution:

The approximate osmolarities are: CT = 300; deepest loop = 1200; DCT = 100; and collecting ducts = 100–1200.

Glossary

countercurrent multiplier system
: involves the descending and ascending loops of Henle directing forming urine in opposing directions to create a concentration gradient when combined with variable permeability and sodium pumping

glycosuria
: presence of glucose in the urine; caused by high blood glucose levels that exceed the ability of the kidneys to reabsorb the glucose; usually the result of untreated or poorly controlled diabetes mellitus

intercalated cell

specialized cell of the collecting ducts that secrete or absorb acid or bicarbonate; important in acid–base balance

leaky tight junctions
: tight junctions in which the sealing strands of proteins between the membranes of adjacent cells are fewer in number and incomplete; allows limited intercellular movement of solvent and solutes

principal cell
: found in collecting ducts and possess channels for the recovery or loss of sodium and potassium; under the control of aldosterone; also have aquaporin channels under ADH control to regulate recovery of water

Regulation of Renal Blood Flow
By the end of this section, you will be able to:

- Describe the myogenic and tubuloglomerular feedback mechanisms and explain how they affect urine volume and composition
- Describe the function of the juxtaglomerular apparatus

It is vital that the flow of blood through the kidney be at a suitable rate to allow for filtration. This rate determines how much solute is retained or discarded, how much water is retained or discarded, and ultimately, the osmolarity of blood and the blood pressure of the body.

Sympathetic Nerves

The kidneys are innervated by the sympathetic neurons of the autonomic nervous system via the celiac plexus and splanchnic nerves. Reduction of sympathetic stimulation results in vasodilation and increased blood flow through the kidneys during resting conditions. When the frequency of action potentials increases, the arteriolar smooth muscle constricts (vasoconstriction), resulting in diminished glomerular flow, so less filtration occurs. Under conditions of stress, sympathetic nervous activity increases, resulting in the direct vasoconstriction of afferent arterioles (norepinephrine effect) as well as stimulation of the adrenal medulla. The adrenal medulla, in turn, produces a generalized vasoconstriction through the release of epinephrine. This includes vasoconstriction of the afferent arterioles, further reducing the volume of blood flowing through the kidneys. This process redirects blood to other organs with more immediate needs. If blood pressure falls, the sympathetic nerves will also stimulate the release of renin. Additional renin increases production of the powerful vasoconstrictor angiotensin II. Angiotensin II, as discussed above, will also stimulate aldosterone production to augment blood volume through retention of more Na^+ and water. Only a 10 mm Hg pressure differential across the glomerulus is required for normal GFR, so very small changes in afferent arterial pressure significantly increase or decrease GFR.

Autoregulation

The kidneys are very effective at regulating the rate of blood flow over a wide range of blood pressures. Your blood pressure will decrease when you are relaxed or sleeping. It will increase when exercising. Yet, despite these changes, the filtration rate through the kidney will change very little. This is due to two internal autoregulatory mechanisms that operate without outside influence: the myogenic mechanism and the tubuloglomerular feedback mechanism.

Arteriole Myogenic Mechanism

The **myogenic mechanism** regulating blood flow within the kidney depends upon a characteristic shared by most smooth muscle cells of the body. When you stretch a smooth muscle cell, it contracts; when you stop, it relaxes, restoring its resting length. This mechanism works in the afferent arteriole that supplies the glomerulus. When blood pressure increases, smooth muscle cells in the wall of the arteriole are stretched and respond by contracting to resist the pressure, resulting in little change in flow. When blood pressure drops, the same smooth muscle cells relax to lower resistance, allowing a continued even flow of blood.

Tubuloglomerular Feedback

The **tubuloglomerular feedback** mechanism involves the JGA and a paracrine signaling mechanism utilizing ATP, adenosine, and nitric oxide (NO). This mechanism stimulates either contraction or relaxation of afferent arteriolar smooth muscle cells ([link]). Recall that the DCT is in intimate contact with the afferent and efferent arterioles of the glomerulus. Specialized macula densa cells in this segment of the tubule respond to changes in the fluid flow rate and Na^+ concentration. As GFR increases, there is less time for NaCl to be reabsorbed in the PCT, resulting in higher osmolarity in the filtrate. The increased fluid movement more strongly deflects single nonmotile cilia on macula densa cells. This increased osmolarity of the forming urine, and the greater flow rate within the DCT, activates macula densa cells to respond by releasing ATP and adenosine (a

metabolite of ATP). ATP and adenosine act locally as paracrine factors to stimulate the myogenic juxtaglomerular cells of the afferent arteriole to constrict, slowing blood flow and reducing GFR. Conversely, when GFR decreases, less Na^+ is in the forming urine, and most will be reabsorbed before reaching the macula densa, which will result in decreased ATP and adenosine, allowing the afferent arteriole to dilate and increase GFR. NO has the opposite effect, relaxing the afferent arteriole at the same time ATP and adenosine are stimulating it to contract. Thus, NO fine-tunes the effects of adenosine and ATP on GFR.

Paracrine Mechanisms Controlling Glomerular Filtration Rate			
Change in GFR	**NaCl Absorption**	**Role of ATP and adenosine/Role of NO**	**Effect on GFR**
Increased GFR	Tubular NaCl increases	ATP and adenosine increase, causing vasoconstriction	Vasoconstriction slows GFR
Decreased GFR	Tubular NaCl decreases	ATP and adenosine decrease, causing vasodilation	Vasodilation increases GFR
Increased GFR	Tubular NaCl increases	NO increases, causing vasodilation	Vasodilation increases GFR

Paracrine Mechanisms Controlling Glomerular Filtration Rate			
Change in GFR	**NaCl Absorption**	**Role of ATP and adenosine/Role of NO**	**Effect on GFR**
Decreased GFR	Tubular NaCl decreases	NO decreases, causing vasoconstricton	Vasoconstriction decreases GFR

Chapter Review

The kidneys are innervated by sympathetic nerves of the autonomic nervous system. Sympathetic nervous activity decreases blood flow to the kidney, making more blood available to other areas of the body during times of stress. The arteriolar myogenic mechanism maintains a steady blood flow by causing arteriolar smooth muscle to contract when blood pressure increases and causing it to relax when blood pressure decreases. Tubuloglomerular feedback involves paracrine signaling at the JGA to cause vasoconstriction or vasodilation to maintain a steady rate of blood flow.

Review Questions

Exercise:

Problem:

Vasodilation of blood vessels to the kidneys is due to ________.

a. more frequent action potentials
b. less frequent action potentials

Solution:

B

Exercise:

Problem:

When blood pressure increases, blood vessels supplying the kidney will _________ to mount a steady rate of filtration.

a. contract
b. relax

Solution:

A

Exercise:

Problem: Which of these three paracrine chemicals cause vasodilation?

a. ATP
b. adenosine
c. nitric oxide

Solution:

C

Critical Thinking Questions

Exercise:

Problem:

Explain what happens to Na^+ concentration in the nephron when GFR increases.

Solution:

Sodium concentration in the filtrate increases when GFR increases; it will decrease when GFR decreases.

Exercise:

Problem:

If you want the kidney to excrete more Na^+ in the urine, what do you want the blood flow to do?

Solution:

To excrete more Na^+ in the urine, increase the flow rate.

Glossary

myogenic mechanism
: mechanism by which smooth muscle responds to stretch by contracting; an increase in blood pressure causes vasoconstriction and a decrease in blood pressure causes vasodilation so that blood flow downstream remains steady

tubuloglomerular feedback
: feedback mechanism involving the JGA; macula densa cells monitor Na^+ concentration in the terminal portion of the ascending loop of Henle and act to cause vasoconstriction or vasodilation of afferent and efferent arterioles to alter GFR

Endocrine Regulation of Kidney Function
By the end of this section, you will be able to:

- Describe how each of the following functions in the extrinsic control of GFR: renin–angiotensin mechanism, natriuretic peptides, and sympathetic adrenergic activity
- Describe how each of the following works to regulate reabsorption and secretion, so as to affect urine volume and composition: renin–angiotensin system, aldosterone, antidiuretic hormone, and natriuretic peptides
- Name and define the roles of other hormones that regulate kidney control

Several hormones have specific, important roles in regulating kidney function. They act to stimulate or inhibit blood flow. Some of these are endocrine, acting from a distance, whereas others are paracrine, acting locally.

Renin–Angiotensin–Aldosterone

Renin is an enzyme that is produced by the granular cells of the afferent arteriole at the JGA. It enzymatically converts angiotensinogen (made by the liver, freely circulating) into angiotensin I. Its release is stimulated by prostaglandins and NO from the JGA in response to decreased extracellular fluid volume.

ACE is not a hormone but it is functionally important in regulating systemic blood pressure and kidney function. It is produced in the lungs but binds to the surfaces of endothelial cells in the afferent arterioles and glomerulus. It enzymatically converts inactive angiotensin I into active angiotensin II. ACE is important in raising blood pressure. People with high blood pressure are sometimes prescribed ACE inhibitors to lower their blood pressure.

Angiotensin II is a potent vasoconstrictor that plays an immediate role in the regulation of blood pressure. It acts systemically to cause vasoconstriction as well as constriction of both the afferent and efferent

arterioles of the glomerulus. In instances of blood loss or dehydration, it reduces both GFR and renal blood flow, thereby limiting fluid loss and preserving blood volume. Its release is usually stimulated by decreases in blood pressure, and so the preservation of adequate blood pressure is its primary role.

Aldosterone, often called the “salt-retaining hormone,” is released from the adrenal cortex in response to angiotensin II or directly in response to increased plasma K^+. It promotes Na^+ reabsorption by the nephron, promoting the retention of water. It is also important in regulating K^+, promoting its excretion. (This dual effect on two minerals and its origin in the adrenal cortex explains its designation as a mineralocorticoid.) As a result, renin has an immediate effect on blood pressure due to angiotensin II–stimulated vasoconstriction and a prolonged effect through Na^+ recovery due to aldosterone. At the same time that aldosterone causes increased recovery of Na^+, it also causes greater loss of K^+. Progesterone is a steroid that is structurally similar to aldosterone. It binds to the aldosterone receptor and weakly stimulates Na^+ reabsorption and increased water recovery. This process is unimportant in men due to low levels of circulating progesterone. It may cause increased retention of water during some periods of the menstrual cycle in women when progesterone levels increase.

Antidiuretic Hormone (ADH)

Diuretics are drugs that can increase water loss by interfering with the recapture of solutes and water from the forming urine. They are often prescribed to lower blood pressure. Coffee, tea, and alcoholic beverages are familiar diuretics. ADH, a 9-amino acid peptide released by the posterior pituitary, works to do the exact opposite. It promotes the recovery of water, decreases urine volume, and maintains plasma osmolarity and blood pressure. It does so by stimulating the movement of aquaporin proteins into the apical cell membrane of principal cells of the collecting ducts to form water channels, allowing the transcellular movement of water from the lumen of the collecting duct into the interstitial space in the medulla of the kidney by osmosis. From there, it enters the vasa recta capillaries to return

to the circulation. Water is attracted by the high osmotic environment of the deep kidney medulla.

Endothelin

Endothelins, 21-amino acid peptides, are extremely powerful vasoconstrictors. They are produced by endothelial cells of the renal blood vessels, mesangial cells, and cells of the DCT. Hormones stimulating endothelin release include angiotensin II, bradykinin, and epinephrine. They do not typically influence blood pressure in healthy people. On the other hand, in people with diabetic kidney disease, endothelin is chronically elevated, resulting in sodium retention. They also diminish GFR by damaging the podocytes and by potently vasoconstricting both the afferent and efferent arterioles.

Natriuretic Hormones

Natriuretic hormones are peptides that stimulate the kidneys to excrete sodium—an effect opposite that of aldosterone. Natriuretic hormones act by inhibiting aldosterone release and therefore inhibiting Na^+ recovery in the collecting ducts. If Na^+ remains in the forming urine, its osmotic force will cause a concurrent loss of water. Natriuretic hormones also inhibit ADH release, which of course will result in less water recovery. Therefore, natriuretic peptides inhibit both Na^+ and water recovery. One example from this family of hormones is atrial natriuretic hormone (ANH), a 28-amino acid peptide produced by heart atria in response to over-stretching of the atrial wall. The over-stretching occurs in persons with elevated blood pressure or heart failure. It increases GFR through concurrent vasodilation of the afferent arteriole and vasoconstriction of the efferent arteriole. These events lead to an increased loss of water and sodium in the forming urine. It also decreases sodium reabsorption in the DCT. There is also B-type natriuretic peptide (BNP) of 32 amino acids produced in the ventricles of the heart. It has a 10-fold lower affinity for its receptor, so its effects are less than those of ANH. Its role may be to provide “fine tuning” for the regulation of blood pressure. BNP’s longer biologic half-life makes it a good diagnostic marker of congestive heart failure ([link]).

Parathyroid Hormone

Parathyroid hormone (PTH) is an 84-amino acid peptide produced by the parathyroid glands in response to decreased circulating Ca^{++} levels. Among its targets is the PCT, where it stimulates the hydroxylation of calcidiol to calcitriol (1,25-hydroxycholecalciferol, the active form of vitamin D). It also blocks reabsorption of phosphate (PO_3^-), causing its loss in the urine. The retention of phosphate would result in the formation of calcium phosphate in the plasma, reducing circulating Ca^{++} levels. By ridding the blood of phosphate, higher circulating Ca^{++} levels are permitted.

Major Hormones That Influence GFR and RFB

	Stimulus	Effect on GFR	Effect on RBF
VASOCONSTRICTORS			
Sympathetic nerves (epinephrine and norepinephrine)	↓ ECFV	↓	↓
Angiotensin II	↓ ECFV	↓	↓
Endothelin	↑ Stretch, bradykinin, angiotensin II, epinephrine ↓ ECFV	↓	↓
VASODILATORS			
Prostaglandins (PGE1, PGE2, and PGI2)	↓ ECFV ↑ shear stress, angiotensin II	No change/↑	↑
Nitric oxide (NO)	↑ shear stress, acetylcholine, histamine, bradykinin, ATP, adenosine	↑	↑
Bradykinin	Prostaglandins, ↓ ACE	↑	↑
Natriuretic peptides (ANP, B-type)	↑ ECFV	↑	No change
ACE = angiotensin-converting enzyme; ECFV = extracellular fluid volume; GFR = glomerular filtration rate; RBF = renal blood flow; ANP = atrial natriuretic peptide; B-type = ventricular natriuretic peptide			

Chapter Review

Endocrine hormones act from a distance and paracrine hormones act locally. The renal enzyme renin converts angiotensinogen into angiotensin I. The lung enzyme, ACE, converts angiotensin I into active angiotensin II. Angiotensin II is an active vasoconstrictor that increases blood pressure. Angiotensin II also stimulates aldosterone release from the adrenal cortex, causing the collecting duct to retain Na^+, which promotes water retention and a longer-term rise in blood pressure. ADH promotes water recovery by

the collecting ducts by stimulating the insertion of aquaporin water channels into cell membranes. Endothelins are elevated in cases of diabetic kidney disease, increasing Na^+ retention and decreasing GFR. Natriuretic hormones, released primarily from the atria of the heart in response to stretching of the atrial walls, stimulate Na^+ excretion and thereby decrease blood pressure. PTH stimulates the final step in the formation of active vitamin D3 and reduces phosphate reabsorption, resulting in higher circulating Ca^{++} levels.

Review Questions

Exercise:

Problem:

What hormone directly opposes the actions of natriuretic hormones?

a. renin
b. nitric oxide
c. dopamine
d. aldosterone

Solution:

D

Exercise:

Problem: Which of these is a vasoconstrictor?

a. nitric oxide
b. natriuretic hormone
c. bradykinin
d. angiotensin II

Solution:

D

Exercise:

Problem:

What signal causes the heart to secrete atrial natriuretic hormone?

a. increased blood pressure
b. decreased blood pressure
c. increased Na^+ levels
d. decreased Na^+ levels

Solution:

A

Critical Thinking Questions

Exercise:

Problem:

What organs produce which hormones or enzymes in the renin–angiotensin system?

Solution:

The liver produces angiotensinogen, the lungs produce ACE, and the kidneys produce renin.

Exercise:

Problem:PTH affects absorption and reabsorption of what?

Solution:

PTH affects absorption and reabsorption of calcium.

Glossary

endothelins
: group of vasoconstrictive, 21-amino acid peptides; produced by endothelial cells of the renal blood vessels, mesangial cells, and cells of the DCT

Regulation of Fluid Volume and Composition
By the end of this section, you will be able to:

- Explain the mechanism of action of diuretics
- Explain why the differential permeability or impermeability of specific sections of the nephron tubules is necessary for urine formation

The major hormones influencing total body water are ADH, aldosterone, and ANH. Circumstances that lead to fluid depletion in the body include blood loss and dehydration. Homeostasis requires that volume and osmolarity be preserved. Blood volume is important in maintaining sufficient blood pressure, and there are nonrenal mechanisms involved in its preservation, including vasoconstriction, which can act within seconds of a drop in pressure. Thirst mechanisms are also activated to promote the consumption of water lost through respiration, evaporation, or urination. Hormonal mechanisms are activated to recover volume while maintaining a normal osmotic environment. These mechanisms act principally on the kidney.

Volume-sensing Mechanisms

The body cannot directly measure blood volume, but blood pressure can be measured. Blood pressure often reflects blood volume and is measured by baroreceptors in the aorta and carotid sinuses. When blood pressure increases, baroreceptors send more frequent action potentials to the central nervous system, leading to widespread vasodilation. Included in this vasodilation are the afferent arterioles supplying the glomerulus, resulting in increased GFR, and water loss by the kidneys. If pressure decreases, fewer action potentials travel to the central nervous system, resulting in more sympathetic stimulation-producing vasoconstriction, which will result in decreased filtration and GFR, and water loss.

Decreased blood pressure is also sensed by the granular cells in the afferent arteriole of the JGA. In response, the enzyme renin is released. You saw earlier in the chapter that renin activity leads to an almost immediate rise in blood pressure as activated angiotensin II produces vasoconstriction. The rise in pressure is sustained by the aldosterone effects initiated by

angiotensin II; this includes an increase in Na^+ retention and water volume. As an aside, late in the menstrual cycle, progesterone has a modest influence on water retention. Due to its structural similarity to aldosterone, progesterone binds to the aldosterone receptor in the collecting duct of the kidney, causing the same, albeit weaker, effect on Na^+ and water retention.

Cardiomyocytes of the atria also respond to greater stretch (as blood pressure rises) by secreting ANH. ANH opposes the action of aldosterone by inhibiting the recovery of Na^+ by the DCT and collecting ducts. More Na^+ is lost, and as water follows, total blood volume and pressure decline. In low-pressure states, ANH does not seem to have much effect.

ADH is also called vasopressin. Early researchers found that in cases of unusually high secretion of ADH, the hormone caused vasoconstriction (vasopressor activity, hence the name). Only later were its antidiuretic properties identified. Synthetic ADH is still used occasionally to stem life-threatening esophagus bleeding in alcoholics.

When blood volume drops 5–10 percent, causing a decrease in blood pressure, there is a rapid and significant increase in ADH release from the posterior pituitary. Immediate vasoconstriction to increase blood pressure is the result. ADH also causes activation of aquaporin channels in the collecting ducts to affect the recovery of water to help restore vascular volume.

Diuretics and Fluid Volume

A **diuretic** is a compound that increases urine volume. Three familiar drinks contain diuretic compounds: coffee, tea, and alcohol. The caffeine in coffee and tea works by promoting vasodilation in the nephron, which increases GFR. Alcohol increases GFR by inhibiting ADH release from the posterior pituitary, resulting in less water recovery by the collecting duct. In cases of high blood pressure, diuretics may be prescribed to reduce blood volume and, thereby, reduce blood pressure. The most frequently prescribed anti-hypertensive diuretic is hydrochlorothiazide. It inhibits the Na^+/ Cl^- symporter in the DCT and collecting duct. The result is a loss of Na^+ with water following passively by osmosis.

Osmotic diuretics promote water loss by osmosis. An example is the indigestible sugar mannitol, which is most often administered to reduce brain swelling after head injury. However, it is not the only sugar that can produce a diuretic effect. In cases of poorly controlled diabetes mellitus, glucose levels exceed the capacity of the tubular glucose symporters, resulting in glucose in the urine. The unrecovered glucose becomes a powerful osmotic diuretic. Classically, in the days before glucose could be detected in the blood and urine, clinicians identified diabetes mellitus by the three Ps: polyuria (diuresis), polydipsia (increased thirst), and polyphagia (increased hunger).

Regulation of Extracellular Na^+

Sodium has a very strong osmotic effect and attracts water. It plays a larger role in the osmolarity of the plasma than any other circulating component of the blood. If there is too much Na^+ present, either due to poor control or excess dietary consumption, a series of metabolic problems ensue. There is an increase in total volume of water, which leads to hypertension (high blood pressure). Over a long period, this increases the risk of serious complications such as heart attacks, strokes, and aneurysms. It can also contribute to system-wide edema (swelling).

Mechanisms for regulating Na^+ concentration include the renin–angiotensin–aldosterone system and ADH (see [link]). Aldosterone stimulates the uptake of Na^+ on the apical cell membrane of cells in the DCT and collecting ducts, whereas ADH helps to regulate Na^+ concentration indirectly by regulating the reabsorption of water.

Regulation of Extracellular K^+

Potassium is present in a 30-fold greater concentration inside the cell than outside the cell. A generalization can be made that K^+ and Na^+ concentrations will move in opposite directions. When more Na^+ is reabsorbed, more K^+ is secreted; when less Na^+ is reabsorbed (leading to excretion by the kidney), more K^+ is retained. When aldosterone causes a recovery of Na^+ in the nephron, a negative electrical gradient is created that promotes the secretion of K^+ and Cl^- into the lumen.

Regulation of Cl^-

Chloride is important in acid–base balance in the extracellular space and has other functions, such as in the stomach, where it combines with hydrogen ions in the stomach lumen to form hydrochloric acid, aiding digestion. Its close association with Na^+ in the extracellular environment makes it the dominant anion of this compartment, and its regulation closely mirrors that of Na^+.

Regulation of Ca^{++} and Phosphate

The parathyroid glands monitor and respond to circulating levels of Ca^{++} in the blood. When levels drop too low, PTH is released to stimulate the DCT to reabsorb Ca^{++} from the forming urine. When levels are adequate or high, less PTH is released and more Ca^{++} remains in the forming urine to be lost. Phosphate levels move in the opposite direction. When Ca^{++} levels are low, PTH inhibits reabsorption of HPO_4^{2-} so that its blood level drops, allowing Ca^{++} levels to rise. PTH also stimulates the renal conversion of calcidiol into calcitriol, the active form of vitamin D. Calcitriol then stimulates the intestines to absorb more Ca^{++} from the diet.

Regulation of H^+, Bicarbonate, and pH

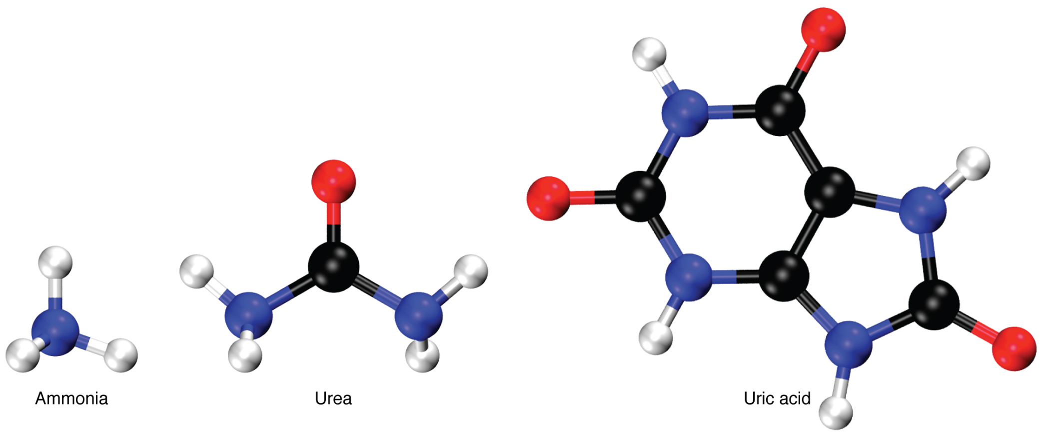
The acid–base homeostasis of the body is a function of chemical buffers and physiologic buffering provided by the lungs and kidneys. Buffers, especially proteins, HCO_3^{2-}, and ammonia have a very large capacity to absorb or release H^+ as needed to resist a change in pH. They can act within fractions of a second. The lungs can rid the body of excess acid very rapidly (seconds to minutes) through the conversion of HCO_3^- into CO_2, which is then exhaled. It is rapid but has limited capacity in the face of a significant acid challenge. The kidneys can rid the body of both acid and base. The renal capacity is large but slow (minutes to hours). The cells of the PCT actively secrete H^+ into the forming urine as Na^+ is reabsorbed. The body rids itself of excess H^+ and raises blood pH. In the collecting ducts, the apical surfaces of intercalated cells have proton pumps that actively secrete H^+ into the luminal, forming urine to remove it from the body.

As hydrogen ions are pumped into the forming urine, it is buffered by bicarbonate (HCO_3^-), $H_2PO_4^-$ (dihydrogen phosphate ion), or ammonia (forming NH_4^+, ammonium ion). Urine pH typically varies in a normal range from 4.5 to 8.0.

Regulation of Nitrogen Wastes

Nitrogen wastes are produced by the breakdown of proteins during normal metabolism. Proteins are broken down into amino acids, which in turn are deaminated by having their nitrogen groups removed. Deamination converts the amino (NH_2) groups into ammonia (NH_3), ammonium ion (NH_4^+), urea, or uric acid ([link]). Ammonia is extremely toxic, so most of it is very rapidly converted into urea in the liver. Human urinary wastes typically contain primarily urea with small amounts of ammonium and very little uric acid.

Nitrogen Wastes



Elimination of Drugs and Hormones

Water-soluble drugs may be excreted in the urine and are influenced by one or all of the following processes: glomerular filtration, tubular secretion, or tubular reabsorption. Drugs that are structurally small can be filtered by the glomerulus with the filtrate. Large drug molecules such as heparin or those that are bound to plasma proteins cannot be filtered and are not readily eliminated. Some drugs can be eliminated by carrier proteins that enable secretion of the drug into the tubule lumen. There are specific carriers that eliminate basic (such as dopamine or histamine) or acidic drugs (such as

penicillin or indomethacin). As is the case with other substances, drugs may be both filtered and reabsorbed passively along a concentration gradient.

Chapter Review

The major hormones regulating body fluids are ADH, aldosterone and ANH. Progesterone is similar in structure to aldosterone and can bind to and weakly stimulate aldosterone receptors, providing a similar but diminished response. Blood pressure is a reflection of blood volume and is monitored by baroreceptors in the aortic arch and carotid sinuses. When blood pressure increases, more action potentials are sent to the central nervous system, resulting in greater vasodilation, greater GFR, and more water lost in the urine. ANH is released by the cardiomyocytes when blood pressure increases, causing Na^+ and water loss. ADH at high levels causes vasoconstriction in addition to its action on the collecting ducts to recover more water. Diuretics increase urine volume. Mechanisms for controlling Na^+ concentration in the blood include the renin–angiotensin–aldosterone system and ADH. When Na^+ is retained, K^+ is excreted; when Na^+ is lost, K^+ is retained. When circulating Ca^{++} decreases, PTH stimulates the reabsorption of Ca^{++} and inhibits reabsorption of HPO_4^{2-}. pH is regulated through buffers, expiration of CO_2, and excretion of acid or base by the kidneys. The breakdown of amino acids produces ammonia. Most ammonia is converted into less-toxic urea in the liver and excreted in the urine. Regulation of drugs is by glomerular filtration, tubular secretion, and tubular reabsorption.

Review Questions

Exercise:

Problem: Which of these beverages does *not* have a diuretic effect?

a. tea
b. coffee
c. alcohol
d. milk

Solution:

D

Exercise:

Problem:

Progesterone can bind to receptors for which hormone that, when released, activates water retention?

a. aldosterone
b. ADH
c. PTH
d. ANH

Solution:

A

Exercise:

Problem: Renin is released in response to ________.

a. increased blood pressure
b. decreased blood pressure
c. ACE
d. diuretics

Solution:

B

Critical Thinking Questions

Exercise:

Problem: Why is ADH also called vasopressin?

Solution:

When first discovered, it was named for its known activity—vasoconstriction.

Exercise:

Problem: How can glucose be a diuretic?

Solution:

In cases of diabetes mellitus, there is more glucose present than the kidney can recover and the excess glucose is lost in the urine. It possesses osmotic character so that it attracts water to the forming urine.

Glossary

diuretic
: compound that increases urine output, leading to decreased water conservation

The Urinary System and Homeostasis
By the end of this section, you will be able to:

- Describe the role of the kidneys in vitamin D activation
- Describe the role of the kidneys in regulating erythropoiesis
- Provide specific examples to demonstrate how the urinary system responds to maintain homeostasis in the body
- Explain how the urinary system relates to other body systems in maintaining homeostasis
- Predict factors or situations affecting the urinary system that could disrupt homeostasis
- Predict the types of problems that would occur in the body if the urinary system could not maintain homeostasis

All systems of the body are interrelated. A change in one system may affect all other systems in the body, with mild to devastating effects. A failure of urinary continence can be embarrassing and inconvenient, but is not life threatening. The loss of other urinary functions may prove fatal. A failure to synthesize vitamin D is one such example.

Vitamin D Synthesis

In order for vitamin D to become active, it must undergo a hydroxylation reaction in the kidney, that is, an –OH group must be added to calcidiol to make calcitriol (1,25-dihydroxycholecalciferol). Activated vitamin D is important for absorption of Ca^{++} in the digestive tract, its reabsorption in the kidney, and the maintenance of normal serum concentrations of Ca^{++} and phosphate. Calcium is vitally important in bone health, muscle contraction, hormone secretion, and neurotransmitter release. Inadequate Ca^{++} leads to disorders like osteoporosis and **osteomalacia** in adults and rickets in children. Deficits may also result in problems with cell proliferation, neuromuscular function, blood clotting, and the inflammatory response. Recent research has confirmed that vitamin D receptors are present in most, if not all, cells of the body, reflecting the systemic importance of vitamin D. Many scientists have suggested it be referred to as a hormone rather than a vitamin.

Erythropoiesis

EPO is a 193-amino acid protein that stimulates the formation of red blood cells in the bone marrow. The kidney produces 85 percent of circulating EPO; the liver, the remainder. If you move to a higher altitude, the partial pressure of oxygen is lower, meaning there is less pressure to push oxygen across the alveolar membrane and into the red blood cell. One way the body compensates is to manufacture more red blood cells by increasing EPO production. If you start an aerobic exercise program, your tissues will need more oxygen to cope, and the kidney will respond with more EPO. If erythrocytes are lost due to severe or prolonged bleeding, or under produced due to disease or severe malnutrition, the kidneys come to the rescue by producing more EPO. Renal failure (loss of EPO production) is associated with anemia, which makes it difficult for the body to cope with increased oxygen demands or to supply oxygen adequately even under normal conditions. Anemia diminishes performance and can be life threatening.

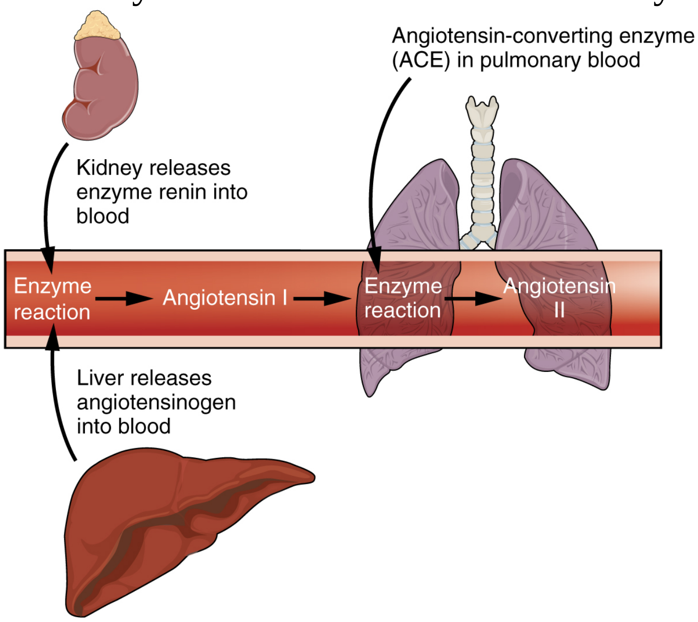
Blood Pressure Regulation

Due to osmosis, water follows where Na^+ leads. Much of the water the kidneys recover from the forming urine follows the reabsorption of Na^+. ADH stimulation of aquaporin channels allows for regulation of water recovery in the collecting ducts. Normally, all of the glucose is recovered, but loss of glucose control (diabetes mellitus) may result in an osmotic dieresis severe enough to produce severe dehydration and death. A loss of renal function means a loss of effective vascular volume control, leading to hypotension (low blood pressure) or hypertension (high blood pressure), which can lead to stroke, heart attack, and aneurysm formation.

The kidneys cooperate with the lungs, liver, and adrenal cortex through the renin–angiotensin–aldosterone system (see [link]). The liver synthesizes and secretes the inactive precursor angiotensinogen. When the blood pressure is low, the kidney synthesizes and releases renin. Renin converts angiotensinogen into angiotensin I, and ACE produced in the lung converts angiotensin I into biologically active angiotensin II ([link]). The immediate and short-term effect of angiotensin II is to raise blood pressure by causing

widespread vasoconstriction. angiotensin II also stimulates the adrenal cortex to release the steroid hormone aldosterone, which results in renal reabsorption of Na^+ and its associated osmotic recovery of water. The reabsorption of Na^+ helps to raise and maintain blood pressure over a longer term.

The Enzyme Renin Converts the Pro-enzyme Angiotensin



Regulation of Osmolarity

Blood pressure and osmolarity are regulated in a similar fashion. Severe hypo-osmolarity can cause problems like lysis (rupture) of blood cells or widespread edema, which is due to a solute imbalance. Inadequate solute concentration (such as protein) in the plasma results in water moving toward an area of greater solute concentration, in this case, the interstitial space and cell cytoplasm. If the kidney glomeruli are damaged by an autoimmune illness, large quantities of protein may be lost in the urine. The resultant drop in serum osmolarity leads to widespread edema that, if severe, may lead to damaging or fatal brain swelling. Severe hypertonic conditions may arise with severe dehydration from lack of water intake, severe vomiting, or uncontrolled diarrhea. When the kidney is unable to recover sufficient water from the forming urine, the consequences may be severe (lethargy, confusion, muscle cramps, and finally, death) .

Recovery of Electrolytes

Sodium, calcium, and potassium must be closely regulated. The role of Na^+ and Ca^{++} homeostasis has been discussed at length. Failure of K^+ regulation can have serious consequences on nerve conduction, skeletal muscle function, and most significantly, on cardiac muscle contraction and rhythm.

pH Regulation

Recall that enzymes lose their three-dimensional conformation and, therefore, their function if the pH is too acidic or basic. This loss of conformation may be a consequence of the breaking of hydrogen bonds. Move the pH away from the optimum for a specific enzyme and you may severely hamper its function throughout the body, including hormone binding, central nervous system signaling, or myocardial contraction. Proper kidney function is essential for pH homeostasis.

Note:
Everyday Connection
Stem Cells and Repair of Kidney Damage
Stem cells are unspecialized cells that can reproduce themselves via cell division, sometimes after years of inactivity. Under certain conditions, they may differentiate into tissue-specific or organ-specific cells with special functions. In some cases, stem cells may continually divide to produce a mature cell and to replace themselves. Stem cell therapy has an enormous potential to improve the quality of life or save the lives of people suffering from debilitating or life-threatening diseases. There have been several studies in animals, but since stem cell therapy is still in its infancy, there have been limited experiments in humans.

Acute kidney injury can be caused by a number of factors, including transplants and other surgeries. It affects 7–10 percent of all hospitalized patients, resulting in the deaths of 35–40 percent of inpatients. In limited studies using mesenchymal stem cells, there have been fewer instances of kidney damage after surgery, the length of hospital stays has been reduced, and there have been fewer readmissions after release.

How do these stem cells work to protect or repair the kidney? Scientists are unsure at this point, but some evidence has shown that these stem cells release several growth factors in endocrine and paracrine ways. As further studies are conducted to assess the safety and effectiveness of stem cell therapy, we will move closer to a day when kidney injury is rare, and curative treatments are routine.

Chapter Review

The effects of failure of parts of the urinary system may range from inconvenient (incontinence) to fatal (loss of filtration and many others). The kidneys catalyze the final reaction in the synthesis of active vitamin D that in turn helps regulate Ca^{++}. The kidney hormone EPO stimulates erythrocyte development and promotes adequate O_2 transport. The kidneys help regulate blood pressure through Na^+ and water retention and loss. The kidneys work with the adrenal cortex, lungs, and liver in the renin–angiotensin–aldosterone system to regulate blood pressure. They regulate osmolarity of the blood by regulating both solutes and water. Three electrolytes are more closely regulated than others: Na^+, Ca^{++}, and K^+. The kidneys share pH regulation with the lungs and plasma buffers, so that proteins can preserve their three-dimensional conformation and thus their function.

Review Questions

Exercise:

Problem:

Which step in vitamin D production does the kidney perform?

a. converts cholecalciferol into calcidiol
b. converts calcidiol into calcitriol
c. stores vitamin D
d. none of these

Solution:

B

Exercise:

Problem:

Which hormone does the kidney produce that stimulates red blood cell production?

a. thrombopoeitin
b. vitamin D
c. EPO
d. renin

Solution:

C

Exercise:

Problem:

If there were no aquaporin channels in the collecting duct, ________.

a. you would develop systemic edema
b. you would retain excess Na^+
c. you would lose vitamins and electrolytes
d. you would suffer severe dehydration

Solution:

D

Critical Thinking Questions

Exercise:

Problem: How does lack of protein in the blood cause edema?

Solution:

Protein has osmotic properties. If there is not enough protein in the blood, water will be attracted to the interstitial space and the cell cytoplasm resulting in tissue edema.

Exercise:

Problem:

Which three electrolytes are most closely regulated by the kidney?

Solution:

The three electrolytes are most closely regulated by the kidney are calcium, sodium, and potassium.

References

Bagul A, Frost JH, Drage M. Stem cells and their role in renal ischaemia reperfusion injury. Am J Nephrol [Internet]. 2013 [cited 2013 Apr 15]; 37(1):16–29. Available from: http://www.karger.com/Article/FullText/345731

Glossary

osteomalacia
: softening of bones due to a lack of mineralization with calcium and phosphate; most often due to lack of vitamin D; in children, osteomalacia is termed rickets; not to be confused with osteoporosis

How Animals Reproduce
By the end of this section, you will be able to:

- Describe advantages and disadvantages of asexual and sexual reproduction
- Discuss asexual reproduction methods
- Discuss sexual reproduction methods
- Discuss internal and external methods of fertilization

Some animals produce offspring through asexual reproduction while other animals produce offspring through sexual reproduction. Both methods have advantages and disadvantages. **Asexual reproduction** produces offspring that are genetically identical to the parent because the offspring are all clones of the original parent. A single individual can produce offspring asexually and large numbers of offspring can be produced quickly; these are two advantages that asexually reproducing organisms have over sexually reproducing organisms. In a stable or predictable environment, asexual reproduction is an effective means of reproduction because all the offspring will be adapted to that environment. In an unstable or unpredictable environment, species that reproduce asexually may be at a disadvantage because all the offspring are genetically identical and may not be adapted to different conditions.

During **sexual reproduction**, the genetic material of two individuals is combined to produce genetically diverse offspring that differ from their parents. The genetic diversity of sexually produced offspring is thought to give sexually reproducing individuals greater fitness because more of their offspring may survive and reproduce in an unpredictable or changing environment. Species that reproduce sexually (and have separate sexes) must maintain two different types of individuals, males and females. Only half the population (females) can produce the offspring, so fewer offspring will be produced when compared to asexual reproduction. This is a disadvantage of sexual reproduction compared to asexual reproduction.

Asexual Reproduction

Asexual reproduction occurs in prokaryotic microorganisms (bacteria and archaea) and in many eukaryotic, single-celled and multi-celled organisms. There are several ways that animals reproduce asexually, the details of which vary among individual species.

Fission

Fission, also called binary fission, occurs in some invertebrate, multi-celled organisms. It is in some ways analogous to the process of binary fission of single-celled prokaryotic organisms. The term fission is applied to instances in which an organism appears to split itself into two parts and, if necessary, regenerate the missing parts of each new organism. For example, species of turbellarian flatworms commonly called the planarians, such as *Dugesia dorotocephala*, are able to separate their bodies into head and tail regions and then regenerate the missing half in each of the two new organisms. Sea anemones (Cnidaria), such as species of the genus *Anthopleura* ([link]), will divide along the oral-aboral axis, and sea cucumbers (Echinodermata) of the genus *Holothuria*, will divide into two halves across the oral-aboral axis and regenerate the other half in each of the resulting individuals.

The *Anthopleura artemisia* sea anemone can reproduce through fission.

Budding

Budding is a form of asexual reproduction that results from the outgrowth of a part of the body leading to a separation of the "bud" from the original organism and the formation of two individuals, one smaller than the other. Budding occurs commonly in some invertebrate animals such as hydras and corals. In hydras, a bud forms that develops into an adult and breaks away from the main body ([link]).

(a) (b)

(a) Hydra reproduce asexually through budding: a bud forms on the tubular body of an adult hydra, develops a mouth and tentacles, and then detaches from its parent. The new hydra is fully developed and will find its own location for attachment. (b) Some coral, such as the *Lophelia pertusa* shown here, can reproduce through budding. (credit b: modification of work by Ed Bowlby, NOAA/Olympic Coast NMS; NOAA/OAR/Office of Ocean Exploration)

Note:
Concept in Action

View this video to see a hydra budding.

Fragmentation

Fragmentation is the breaking of an individual into parts followed by regeneration. If the animal is capable of fragmentation, and the parts are big enough, a separate individual will regrow from each part. Fragmentation may occur through accidental damage, damage from predators, or as a natural form of reproduction. Reproduction through fragmentation is observed in sponges, some cnidarians, turbellarians, echinoderms, and annelids. In some sea stars, a new individual can be regenerated from a broken arm and a piece of the central disc. This sea star ([link]) is in the process of growing a complete sea star from an arm that has been cut off. Fisheries workers have been known to try to kill the sea stars eating their clam or oyster beds by cutting them in half and throwing them back into the ocean. Unfortunately for the workers, the two parts can each regenerate a new half, resulting in twice as many sea stars to prey upon the oysters and clams.

(a) *Linckia multifora* is a species of sea star that can reproduce asexually via fragmentation. In this process, (b) an arm that has been shed grows into a new sea star. (credit a: modifiction of work by Dwayne Meadows, NOAA/NMFS/OPR)

Parthenogenesis

Parthenogenesis is a form of asexual reproduction in which an egg develops into an individual without being fertilized. The resulting offspring can be either haploid or diploid, depending on the process in the species. Parthenogenesis occurs in invertebrates such as water fleas, rotifers, aphids, stick insects, and ants, wasps, and bees. Ants, bees, and wasps use parthenogenesis to produce haploid males (drones). The diploid females (workers and queens) are the result of a fertilized egg.

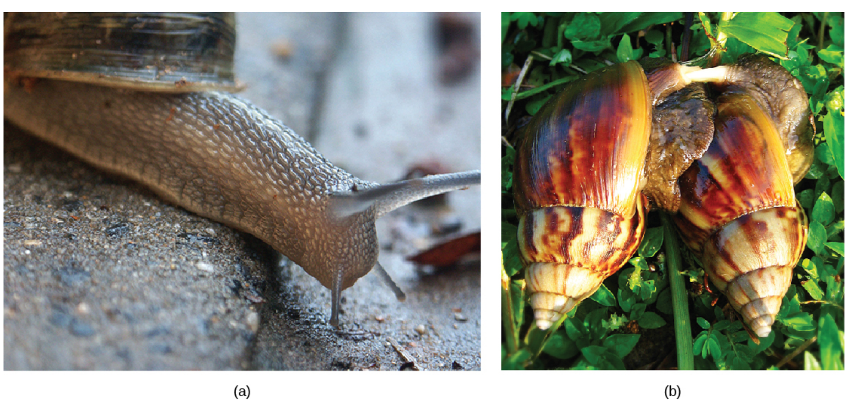
Some vertebrate animals—such as certain reptiles, amphibians, and fish—also reproduce through parthenogenesis. Parthenogenesis has been observed in species in which the sexes were separated in terrestrial or marine zoos. Two female Komodo dragons, a hammerhead shark, and a blacktop shark have produced parthenogenic young when the females have been isolated from males. It is possible that the asexual reproduction observed occurred in response to unusual circumstances and would normally not occur.

Sexual Reproduction

Sexual reproduction is the combination of reproductive cells from two individuals to form genetically unique offspring. The nature of the individuals that produce the two kinds of gametes can vary, having for example separate sexes or both sexes in each individual. Sex determination, the mechanism that determines which sex an individual develops into, also can vary.

Hermaphroditism

Hermaphroditism occurs in animals in which one individual has both male and female reproductive systems. Invertebrates such as earthworms, slugs, tapeworms, and snails ([link]) are often hermaphroditic. Hermaphrodites may self-fertilize, but typically they will mate with another of their species, fertilizing each other and both producing offspring. Self-fertilization is more common in animals that have limited mobility or are not motile, such as barnacles and clams. Many species have specific mechanisms in place to prevent self-fertilization, because it is an extreme form of inbreeding and usually produces less fit offspring.



Many (a) snails are hermaphrodites. When two individuals (b) mate, they can produce up to 100 eggs each. (credit a: modification of work

by Assaf Shtilman; credit b: modification of work by "Schristia"/Flickr)

Sex Determination

Mammalian sex is determined genetically by the combination of X and Y chromosomes. Individuals homozygous for X (XX) are female and heterozygous individuals (XY) are male. In mammals, the presence of a Y chromosome causes the development of male characteristics and its absence results in female characteristics. The XY system is also found in some insects and plants.

Bird **sex determination** is dependent on the combination of Z and W chromosomes. Homozygous for Z (ZZ) results in a male and heterozygous (ZW) results in a female. Notice that this system is the opposite of the mammalian system because in birds the female is the sex with the different sex chromosomes. The W appears to be essential in determining the sex of the individual, similar to the Y chromosome in mammals. Some fish, crustaceans, insects (such as butterflies and moths), and reptiles use the ZW system.

More complicated chromosomal sex determining systems also exist. For example, some swordtail fish have three sex chromosomes in a population.

The sex of some other species is not determined by chromosomes, but by some aspect of the environment. Sex determination in alligators, some turtles, and tuataras, for example, is dependent on the temperature during the middle third of egg development. This is referred to as environmental sex determination, or more specifically, as temperature-dependent sex determination. In many turtles, cooler temperatures during egg incubation produce males and warm temperatures produce females, while in many other species of turtles, the reverse is true. In some crocodiles and some turtles, moderate temperatures produce males and both warm and cool temperatures produce females.

Individuals of some species change their sex during their lives, switching from one to the other. If the individual is female first, it is termed protogyny or “first female,” if it is male first, it is termed protandry or “first male.” Oysters are born male, grow in size, and become female and lay eggs. The wrasses, a family of reef fishes, are all sequential hermaphrodites. Some of these species live in closely coordinated schools with a dominant male and a large number of smaller females. If the male dies, a female increases in size, changes sex, and becomes the new dominant male.

Fertilization

The fusion of a sperm and an egg is a process called fertilization. This can occur either inside (**internal fertilization**) or outside (**external fertilization**) the body of the female. Humans provide an example of the former, whereas frog reproduction is an example of the latter.

External Fertilization

External fertilization usually occurs in aquatic environments where both eggs and sperm are released into the water. After the sperm reaches the egg, fertilization takes place. Most external fertilization happens during the process of spawning where one or several females release their eggs and the male(s) release sperm in the same area, at the same time. The spawning may be triggered by environmental signals, such as water temperature or the length of daylight. Nearly all fish spawn, as do crustaceans (such as crabs and shrimp), mollusks (such as oysters), squid, and echinoderms (such as sea urchins and sea cucumbers). Revise to "Frogs, corals, squid, and octopuses also spawn ([link]).

During sexual reproduction in toads, the male grasps the female from behind and externally fertilizes the eggs as they are deposited. (credit: Bernie Kohl)

Internal Fertilization

Internal fertilization occurs most often in terrestrial animals, although some aquatic animals also use this method. Internal fertilization may occur by the male directly depositing sperm in the female during mating. It may also occur by the male depositing sperm in the environment, usually in a protective structure, which a female picks up to deposit the sperm in her reproductive tract. There are three ways that offspring are produced following internal fertilization. In **oviparity**, fertilized eggs are laid outside the female's body and develop there, receiving nourishment from the yolk that is a part of the egg ([link]**a**). This occurs in some bony fish, some reptiles, a few cartilaginous fish, some amphibians, a few mammals, and all birds. Most non-avian reptiles and insects produce leathery eggs, while birds and some turtles produce eggs with high concentrations of calcium carbonate in the shell, making them hard. Chicken eggs are an example of a hard shell. The eggs of the egg-laying mammals such as the platypus and echidna are leathery.

In **oviparity**, fertilized eggs are retained in the female, and the embryo obtains its nourishment from the egg's yolk. The eggs are retained in the female's body until they hatch inside of her, or she lays the eggs right before they hatch. This process helps protect the eggs until hatching. This occurs in some bony fish (like the platyfish *Xiphophorus maculatus*, [link]**b**), some sharks, lizards, some snakes (garter snake *Thamnophis sirtalis*), some vipers, and some invertebrate animals (Madagascar hissing cockroach *Gromphadorhina portentosa*).

In **viviparity** the young are born alive. They obtain their nourishment from the female and are born in varying states of maturity. This occurs in most mammals ([link]**c**), some cartilaginous fish, and a few reptiles.

(a) (b) (c)

In (a) oviparity, young develop in eggs outside the female body, as with these *Harmonia axydridis* beetles hatching. Some aquatic animals, like this (b) pregnant *Xiphophorus maculatus* are ovoviparous, with the egg developing inside the female and nutrition supplied primarily from the yolk. In mammals, nutrition is supported by the placenta, as was the case with this (c) newborn squirrel. (credit b: modification of work by Gourami Watcher; credit c: modification of work by "audreyjm529"/Flickr)

Section Summary

Reproduction may be asexual when one individual produces genetically identical offspring, or sexual when the genetic material from two individuals is combined to produce genetically diverse offspring. Asexual reproduction in animals occurs through fission, budding, fragmentation, and parthenogenesis. Sexual reproduction may involve fertilization inside the body or in the external environment. A species may have separate sexes or combined sexes; when the sexes are combined they may be expressed at different times in the life cycle. The sex of an individual may be determined by various chromosomal systems or environmental factors such as temperature.

Sexual reproduction starts with the combination of a sperm and an egg in a process called fertilization. This can occur either outside the bodies or inside the female. The method of fertilization varies among animals. Some species release the egg and sperm into the environment, some species retain the egg and receive the sperm into the female body and then expel the developing embryo covered with shell, while still other species retain the developing offspring throughout the gestation period.

Review Questions

Exercise:

Problem: In which group is parthenogenesis a normal event?

a. chickens
b. bees
c. rabbits
d. sea stars

Solution:

B

Exercise:

Problem:

Genetically unique individuals are produced through ________.

a. sexual reproduction
b. parthenogenesis
c. budding
d. fragmentation

Solution:

A

Exercise:

Problem: External fertilization occurs in which type of environment?

a. aquatic
b. forested
c. savanna
d. steppe

Solution:

A

Free Response

Exercise:

Problem:

What might be a disadvantage to temperature-dependent sex determination?

Solution:

Temperatures can vary from year to year and an unusually cold or hot year might produce offspring all of one sex, making it hard for individuals to find mates.

Exercise:

Problem:

Compared to separate sexes and assuming self-fertilizing is not possible, what might be one advantage and one disadvantage to hermaphroditism?

Solution:

A possible advantage of hermaphroditism might be that anytime an individual of the same species is encountered a mating is possible, unlike separate sexes that must find an individual of the right sex to mate. (Also, every individual in a hermaphrodite population is able to produce offspring, which is not the case in populations with separate sexes.) A disadvantage might be that hermaphrodite populations are less efficient because they do not specialize in one sex or another, which means a hermaphrodite does not produce as many offspring through eggs or sperm as do species with separate sexes. (Other answers are possible.)

Glossary

asexual reproduction
: a mechanism that produces offspring that are genetically identical to the parent

budding
: a form of asexual reproduction that results from the outgrowth of a part of an organism leading to a separation from the original animal into two individuals

external fertilization

the fertilization of eggs by sperm outside an animal’s body, often during spawning

fission
(also, binary fission) a form of asexual reproduction in which an organism splits into two separate organisms or two parts that regenerate the missing portions of the body

fragmentation
the breaking of an organism into parts and the growth of a separate individual from each part

hermaphroditism
the state of having both male and female reproductive structures within the same individual

internal fertilization
the fertilization of eggs by sperm inside the body of the female

oviparity
a process by which fertilized eggs are laid outside the female’s body and develop there, receiving nourishment from the yolk that is a part of the egg

ovoviparity
a process by which fertilized eggs are retained within the female; the embryo obtains its nourishment from the egg’s yolk, and the young are fully developed when they are hatched

parthenogenesis
a form of asexual reproduction in which an egg develops into a complete individual without being fertilized

sex determination
the mechanism by which the sex of individuals in sexually reproducing organisms is initially established

sexual reproduction

a form of reproduction in which cells containing genetic material from two individuals combines to produce genetically unique offspring

viviparity
: a process in which the young develop within the female and are born in a nonembryonic state

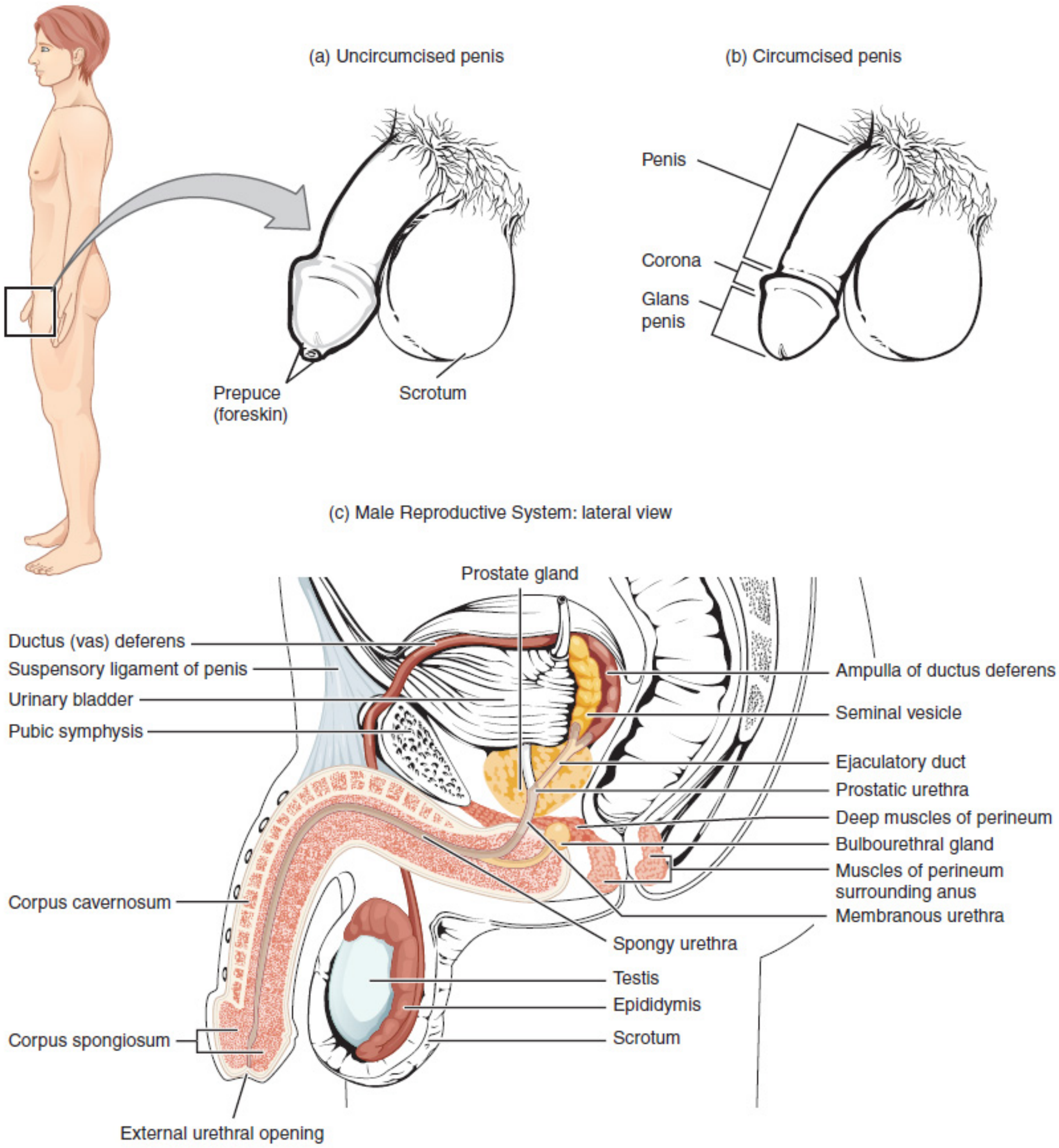
Anatomy and Physiology of the Male Reproductive System

By the end of this section, you will be able to:

- Describe the structure and function of the organs of the male reproductive system
- Describe the structure and function of the sperm cell
- Explain the events during spermatogenesis that produce haploid sperm from diploid cells
- Identify the importance of testosterone in male reproductive function

Unique for its role in human reproduction, a **gamete** is a specialized sex cell carrying 23 chromosomes—one half the number in body cells. At fertilization, the chromosomes in one male gamete, called a **sperm** (or spermatozoon), combine with the chromosomes in one female gamete, called an oocyte. The function of the male reproductive system ([link]) is to produce sperm and transfer them to the female reproductive tract. The paired testes are a crucial component in this process, as they produce both sperm and androgens, the hormones that support male reproductive physiology. In humans, the most important male androgen is testosterone. Several accessory organs and ducts aid the process of sperm maturation and transport the sperm and other seminal components to the penis, which delivers sperm to the female reproductive tract. In this section, we examine each of these different structures, and discuss the process of sperm production and transport.

Male Reproductive System



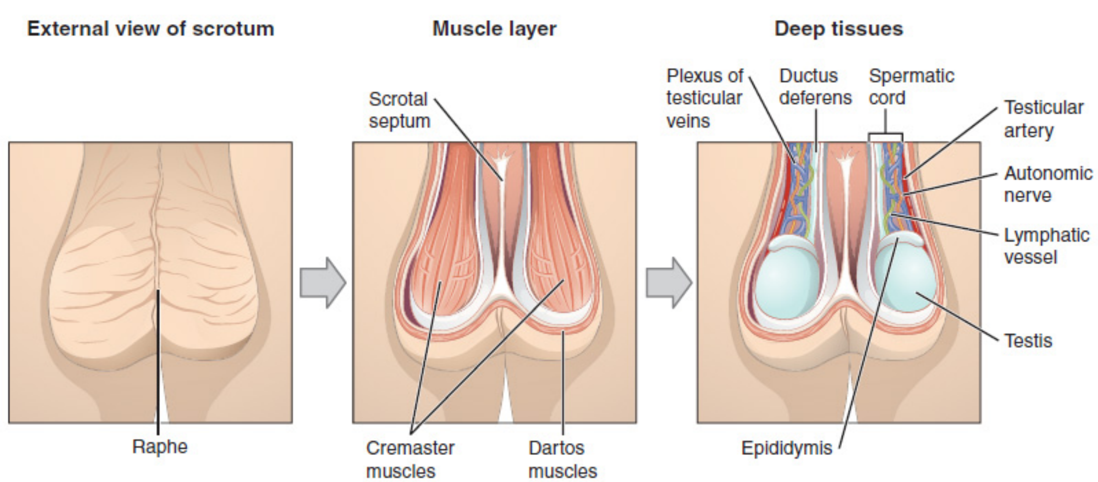
The structures of the male reproductive system include the testes, the epididymides, the penis, and the ducts and glands that produce and carry semen. Sperm exit the scrotum through the ductus deferens, which is bundled in the spermatic cord. The seminal vesicles and prostate gland add fluids to the sperm to create semen.

Scrotum

The testes are located in a skin-covered, highly pigmented, muscular sack called the **scrotum** that extends from the body behind the penis (see [link]). This location is important in sperm production, which occurs within the testes, and proceeds more efficiently when the testes are kept 2 to 4°C below core body temperature.

The dartos muscle makes up the subcutaneous muscle layer of the scrotum ([link]). It continues internally to make up the scrotal septum, a wall that divides the scrotum into two compartments, each housing one testis. Descending from the internal oblique muscle of the abdominal wall are the two cremaster muscles, which cover each testis like a muscular net. By contracting simultaneously, the dartos and cremaster muscles can elevate the testes in cold weather (or water), moving the testes closer to the body and decreasing the surface area of the scrotum to retain heat. Alternatively, as the environmental temperature increases, the scrotum relaxes, moving the testes farther from the body core and increasing scrotal surface area, which promotes heat loss. Externally, the scrotum has a raised medial thickening on the surface called the raphae.

The Scrotum and Testes



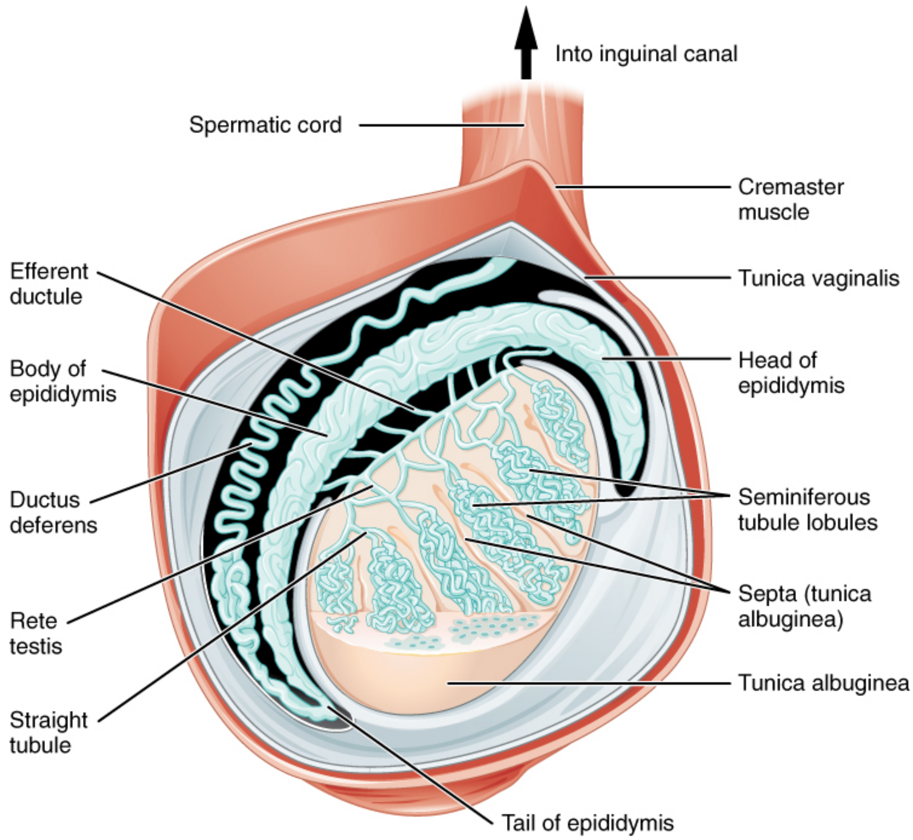
This anterior view shows the structures of the scrotum and testes.

Testes

The **testes** (singular = testis) are the male **gonads**—that is, the male reproductive organs. They produce both sperm and androgens, such as testosterone, and are active throughout the reproductive lifespan of the male.

Paired ovals, the testes are each approximately 4 to 5 cm in length and are housed within the scrotum (see [link]). They are surrounded by two distinct layers of protective connective tissue ([link]). The outer tunica vaginalis is a serous membrane that has both a parietal and a thin visceral layer. Beneath the tunica vaginalis is the tunica albuginea, a tough, white, dense connective tissue layer covering the testis itself. Not only does the tunica albuginea cover the outside of the testis, it also invaginates to form septa that divide the testis into 300 to 400 structures called lobules. Within the lobules, sperm develop in structures called seminiferous tubules. During the seventh month of the developmental period of a male fetus, each testis moves through the abdominal musculature to descend into the scrotal cavity. This is called the “descent of the testis.” Cryptorchidism is the clinical term used when one or both of the testes fail to descend into the scrotum prior to birth.

Anatomy of the Testis



This sagittal view shows the seminiferous tubules, the site of sperm production. Formed sperm are transferred to the epididymis, where they mature. They leave the epididymis during an ejaculation via the ductus deferens.

The tightly coiled **seminiferous tubules** form the bulk of each testis. They are composed of developing sperm cells surrounding a lumen, the hollow center of the tubule, where formed sperm are released into the duct system of the testis. Specifically, from the lumens of the seminiferous tubules, sperm move into the straight tubules (or tubuli recti), and from there into a fine meshwork of tubules called the rete testes. Sperm leave the rete testes, and the testis itself, through the 15 to 20 efferent ductules that cross the tunica albuginea.

Inside the seminiferous tubules are six different cell types. These include supporting cells called sustentacular cells, as well as five types of developing sperm cells called germ cells. Germ cell development progresses from the basement membrane—at the perimeter of the tubule—toward the lumen. Let’s look more closely at these cell types.

Sertoli Cells

Surrounding all stages of the developing sperm cells are elongate, branching **Sertoli cells**. Sertoli cells are a type of supporting cell called a sustentacular cell, or sustentocyte, that are typically found in epithelial tissue. Sertoli cells secrete signaling molecules that promote sperm production and can control whether germ cells live or die. They extend physically around the germ cells from the peripheral basement membrane of the seminiferous tubules to the lumen. Tight junctions between these sustentacular cells create the **blood–testis barrier**, which keeps bloodborne substances from reaching the germ cells and, at the same time, keeps surface antigens on developing germ cells from escaping into the bloodstream and prompting an autoimmune response.

Germ Cells

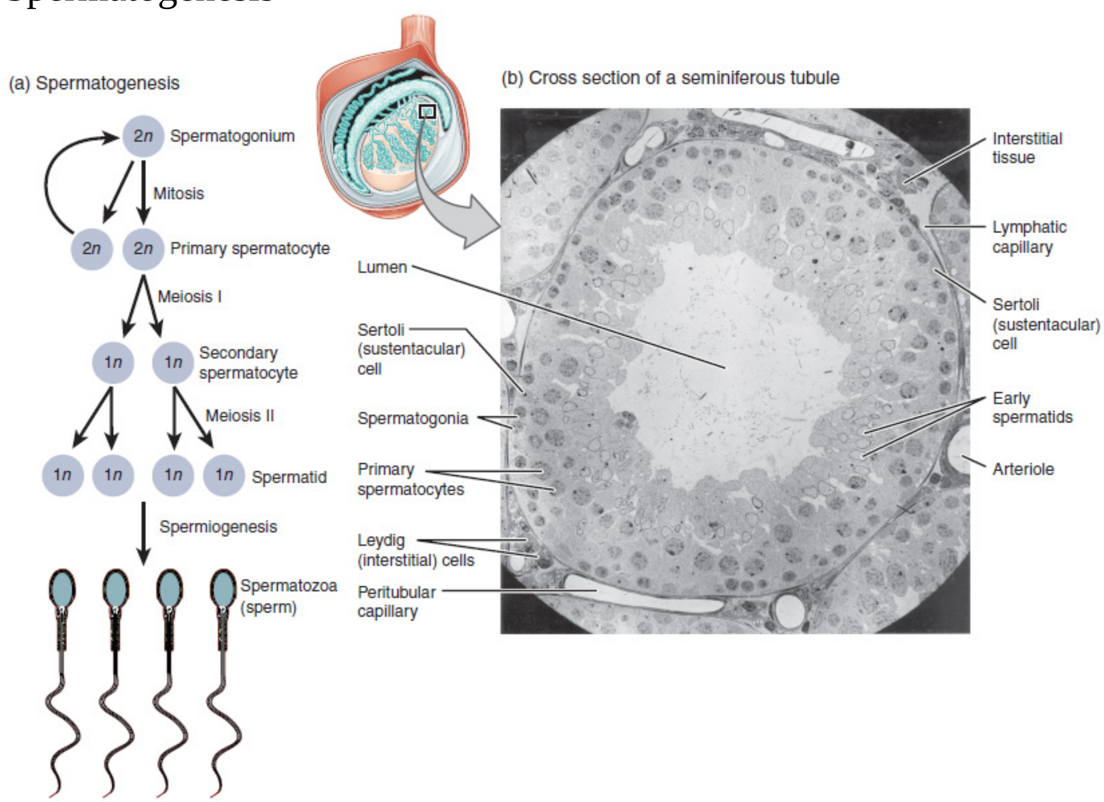
The least mature cells, the **spermatogonia** (singular = spermatogonium), line the basement membrane inside the tubule. Spermatogonia are the stem cells of the testis, which means that they are still able to differentiate into a variety of different cell types throughout adulthood. Spermatogonia divide to produce primary and secondary spermatocytes, then spermatids, which finally produce formed sperm. The process that begins with spermatogonia and concludes with the production of sperm is called **spermatogenesis**.

Spermatogenesis

As just noted, spermatogenesis occurs in the seminiferous tubules that form the bulk of each testis (see [link]). The process begins at puberty, after which time sperm are produced constantly throughout a man's life. One production cycle, from spermatogonia through formed sperm, takes approximately 64 days. A new cycle starts approximately every 16 days, although this timing is not synchronous across the seminiferous tubules. Sperm counts—the total number of sperm a man produces—slowly decline after age 35, and some studies suggest that smoking can lower sperm counts irrespective of age.

The process of spermatogenesis begins with mitosis of the diploid spermatogonia ([link]). Because these cells are diploid (2*n*), they each have a complete copy of the father's genetic material, or 46 chromosomes. However, mature gametes are haploid (1*n*), containing 23 chromosomes—meaning that daughter cells of spermatogonia must undergo a second cellular division through the process of meiosis.

Spermatogenesis



(a) Mitosis of a spermatogonial stem cell involves a single cell division that results in two identical, diploid daughter cells

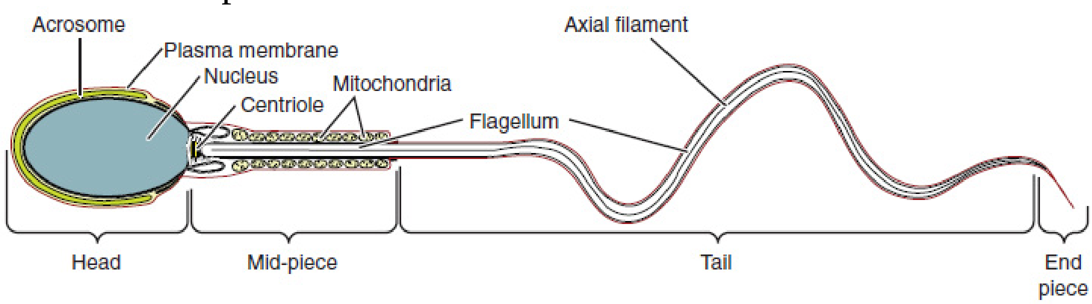
(spermatogonia to primary spermatocyte). Meiosis has two rounds of cell division: primary spermatocyte to secondary spermatocyte, and then secondary spermatocyte to spermatid. This produces four haploid daughter cells (spermatids). (b) In this electron micrograph of a cross-section of a seminiferous tubule from a rat, the lumen is the light-shaded area in the center of the image. The location of the primary spermatocytes is near the basement membrane, and the early spermatids are approaching the lumen (tissue source: rat). EM × 900. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Two identical diploid cells result from spermatogonia mitosis. One of these cells remains a spermatogonium, and the other becomes a primary **spermatocyte**, the next stage in the process of spermatogenesis. As in mitosis, DNA is replicated in a primary spermatocyte, before it undergoes a cell division called meiosis I. During meiosis I each of the 23 pairs of chromosomes separates. This results in two cells, called secondary spermatocytes, each with only half the number of chromosomes. Now a second round of cell division (meiosis II) occurs in both of the secondary spermatocytes. During meiosis II each of the 23 replicated chromosomes divides, similar to what happens during mitosis. Thus, meiosis results in separating the chromosome pairs. This second meiotic division results in a total of four cells with only half of the number of chromosomes. Each of these new cells is a **spermatid**. Although haploid, early spermatids look very similar to cells in the earlier stages of spermatogenesis, with a round shape, central nucleus, and large amount of cytoplasm. A process called **spermiogenesis** transforms these early spermatids, reducing the cytoplasm, and beginning the formation of the parts of a true sperm. The fifth stage of germ cell formation—spermatozoa, or formed sperm—is the end result of this process, which occurs in the portion of the tubule nearest the lumen. Eventually, the sperm are released into the lumen and are moved along a series of ducts in the testis toward a structure called the epididymis for the next step of sperm maturation.

Structure of Formed Sperm

Sperm are smaller than most cells in the body; in fact, the volume of a sperm cell is 85,000 times less than that of the female gamete. Approximately 100 to 300 million sperm are produced each day, whereas women typically ovulate only one oocyte per month. As is true for most cells in the body, the structure of sperm cells speaks to their function. Sperm have a distinctive head, mid-piece, and tail region ([link]). The head of the sperm contains the extremely compact haploid nucleus with very little cytoplasm. These qualities contribute to the overall small size of the sperm (the head is only 5 μm long). A structure called the acrosome covers most of the head of the sperm cell as a “cap” that is filled with lysosomal enzymes important for preparing sperm to participate in fertilization. Tightly packed mitochondria fill the mid-piece of the sperm. ATP produced by these mitochondria will power the flagellum, which extends from the neck and the mid-piece through the tail of the sperm, enabling it to move the entire sperm cell. The central strand of the flagellum, the axial filament, is formed from one centriole inside the maturing sperm cell during the final stages of spermatogenesis.

Structure of Sperm



Sperm cells are divided into a head, containing DNA; a mid-piece, containing mitochondria; and a tail, providing motility. The acrosome is oval and somewhat flattened.

Sperm Transport

To fertilize an egg, sperm must be moved from the seminiferous tubules in the testes, through the epididymis, and—later during ejaculation—along the length of the penis and out into the female reproductive tract.

Role of the Epididymis

From the lumen of the seminiferous tubules, the immotile sperm are surrounded by testicular fluid and moved to the **epididymis** (plural = epididymides), a coiled tube attached to the testis where newly formed sperm continue to mature (see [link]). Though the epididymis does not take up much room in its tightly coiled state, it would be approximately 6 m (20 feet) long if straightened. It takes an average of 12 days for sperm to move through the coils of the epididymis, with the shortest recorded transit time in humans being one day. Sperm enter the head of the epididymis and are moved along predominantly by the contraction of smooth muscles lining the epididymal tubes. As they are moved along the length of the epididymis, the sperm further mature and acquire the ability to move under their own power. Once inside the female reproductive tract, they will use this ability to move independently toward the unfertilized egg. The more mature sperm are then stored in the tail of the epididymis (the final section) until ejaculation occurs.

Duct System

During ejaculation, sperm exit the tail of the epididymis and are pushed by smooth muscle contraction to the **ductus deferens** (also called the vas deferens). The ductus deferens is a thick, muscular tube that is bundled together inside the scrotum with connective tissue, blood vessels, and nerves into a structure called the **spermatic cord** (see [link] and [link]). Because the ductus deferens is physically accessible within the scrotum, surgical sterilization to interrupt sperm delivery can be performed by cutting and sealing a small section of the ductus (vas) deferens. This procedure is called a vasectomy, and it is an effective form of male birth control. Although it may be possible to reverse a vasectomy, clinicians

consider the procedure permanent, and advise men to undergo it only if they are certain they no longer wish to father children.

Note:
Interactive Link Feature

Watch this video to learn about a vasectomy. As described in this video, a vasectomy is a procedure in which a small section of the ductus (vas) deferens is removed from the scrotum. This interrupts the path taken by sperm through the ductus deferens. If sperm do not exit through the vas, either because the man has had a vasectomy or has not ejaculated, in what region of the testis do they remain?

From each epididymis, each ductus deferens extends superiorly into the abdominal cavity through the **inguinal canal** in the abdominal wall. From here, the ductus deferens continues posteriorly to the pelvic cavity, ending posterior to the bladder where it dilates in a region called the ampulla (meaning “flask”).

Sperm make up only 5 percent of the final volume of **semen**, the thick, milky fluid that the male ejaculates. The bulk of semen is produced by three critical accessory glands of the male reproductive system: the seminal vesicles, the prostate, and the bulbourethral glands.

Seminal Vesicles

As sperm pass through the ampulla of the ductus deferens at ejaculation, they mix with fluid from the associated **seminal vesicle** (see [link]). The paired seminal vesicles are glands that contribute approximately 60 percent of the semen volume. Seminal vesicle fluid contains large amounts of fructose, which is used by the sperm mitochondria to generate ATP to allow movement through the female reproductive tract.

The fluid, now containing both sperm and seminal vesicle secretions, next moves into the associated **ejaculatory duct**, a short structure formed from the ampulla of the ductus deferens and the duct of the seminal vesicle. The paired ejaculatory ducts transport the seminal fluid into the next structure, the prostate gland.

Prostate Gland

As shown in [link], the centrally located **prostate gland** sits anterior to the rectum at the base of the bladder surrounding the prostatic urethra (the portion of the urethra that runs within the prostate). About the size of a walnut, the prostate is formed of both muscular and glandular tissues. It excretes an alkaline, milky fluid to the passing seminal fluid—now called semen—that is critical to first coagulate and then decoagulate the semen following ejaculation. The temporary thickening of semen helps retain it within the female reproductive tract, providing time for sperm to utilize the fructose provided by seminal vesicle secretions. When the semen regains its fluid state, sperm can then pass farther into the female reproductive tract.

The prostate normally doubles in size during puberty. At approximately age 25, it gradually begins to enlarge again. This enlargement does not usually cause problems; however, abnormal growth of the prostate, or benign prostatic hyperplasia (BPH), can cause constriction of the urethra as it passes through the middle of the prostate gland, leading to a number of lower urinary tract symptoms, such as a frequent and intense urge to urinate, a weak stream, and a sensation that the bladder has not emptied completely. By age 60, approximately 40 percent of men have some degree of BPH. By age 80, the number of affected individuals has jumped to as many as 80 percent. Treatments for BPH attempt to relieve the pressure on

the urethra so that urine can flow more normally. Mild to moderate symptoms are treated with medication, whereas severe enlargement of the prostate is treated by surgery in which a portion of the prostate tissue is removed.

Another common disorder involving the prostate is prostate cancer. According to the Centers for Disease Control and Prevention (CDC), prostate cancer is the second most common cancer in men. However, some forms of prostate cancer grow very slowly and thus may not ever require treatment. Aggressive forms of prostate cancer, in contrast, involve metastasis to vulnerable organs like the lungs and brain. There is no link between BPH and prostate cancer, but the symptoms are similar. Prostate cancer is detected by a medical history, a blood test, and a rectal exam that allows physicians to palpate the prostate and check for unusual masses. If a mass is detected, the cancer diagnosis is confirmed by biopsy of the cells.

Bulbourethral Glands

The final addition to semen is made by two **bulbourethral glands** (or Cowper’s glands) that release a thick, salty fluid that lubricates the end of the urethra and the vagina, and helps to clean urine residues from the penile urethra. The fluid from these accessory glands is released after the male becomes sexually aroused, and shortly before the release of the semen. It is therefore sometimes called pre-ejaculate. It is important to note that, in addition to the lubricating proteins, it is possible for bulbourethral fluid to pick up sperm already present in the urethra, and therefore it may be able to cause pregnancy.

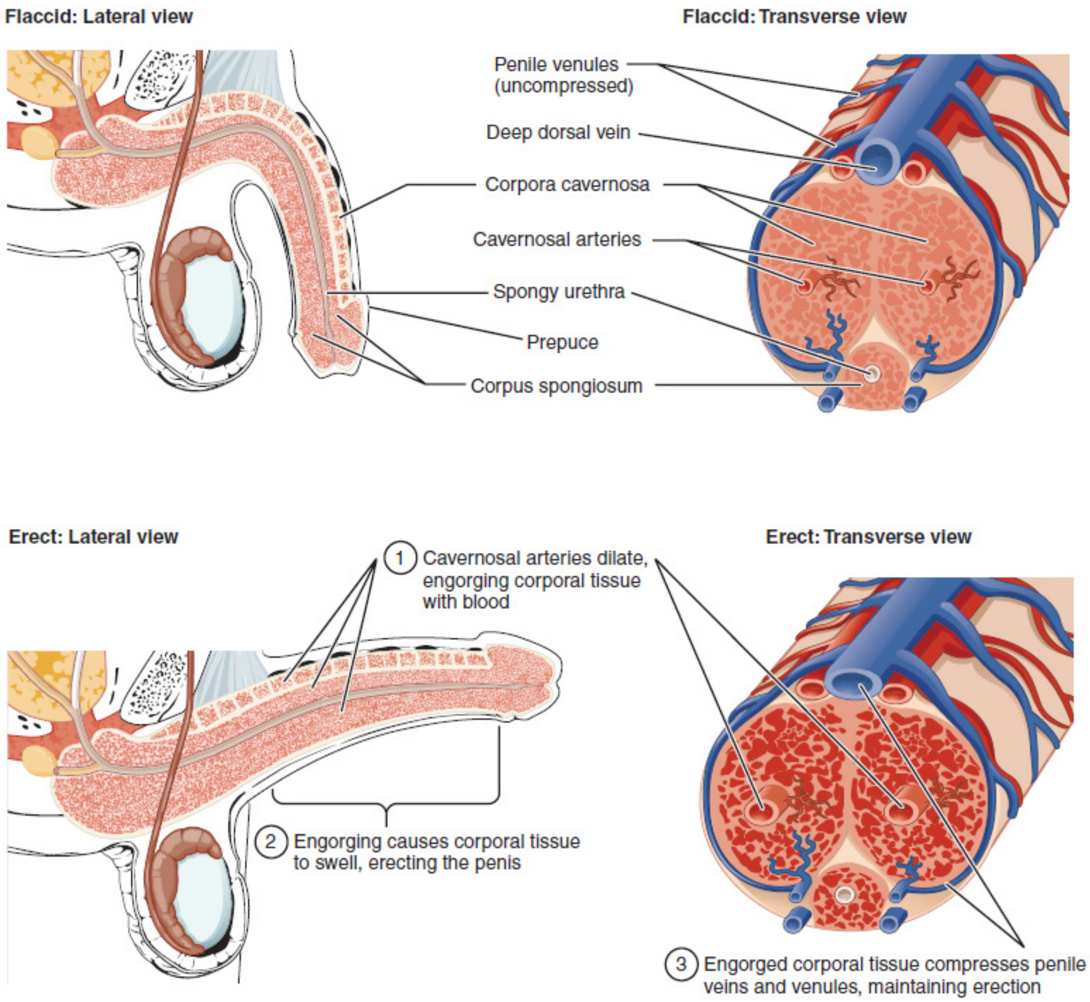
Note:
Interactive Link Feature

Watch this video to explore the structures of the male reproductive system and the path of sperm, which starts in the testes and ends as the sperm leave the penis through the urethra. Where are sperm deposited after they leave the ejaculatory duct?

The Penis

The **penis** is the male organ of copulation (sexual intercourse). It is flaccid for non-sexual actions, such as urination, and turgid and rod-like with sexual arousal. When erect, the stiffness of the organ allows it to penetrate into the vagina and deposit semen into the female reproductive tract.

Cross-Sectional Anatomy of the Penis



Three columns of erectile tissue make up most of the volume of the penis.

The shaft of the penis surrounds the urethra ([link]). The shaft is composed of three column-like chambers of erectile tissue that span the length of the shaft. Each of the two larger lateral chambers is called a **corpus cavernosum** (plural = corpora cavernosa). Together, these make up the bulk of the penis. The **corpus spongiosum**, which can be felt as a raised ridge on the erect penis, is a smaller chamber that surrounds the spongy, or penile, urethra. The end of the penis, called the **glans penis**, has a high concentration of nerve endings, resulting in very sensitive skin that influences the likelihood of ejaculation (see [link]). The skin from the shaft

extends down over the glans and forms a collar called the **prepuce** (or foreskin). The foreskin also contains a dense concentration of nerve endings, and both lubricate and protect the sensitive skin of the glans penis. A surgical procedure called circumcision, often performed for religious or social reasons, removes the prepuce, typically within days of birth.

Both sexual arousal and REM sleep (during which dreaming occurs) can induce an erection. Penile erections are the result of vasocongestion, or engorgement of the tissues because of more arterial blood flowing into the penis than is leaving in the veins. During sexual arousal, nitric oxide (NO) is released from nerve endings near blood vessels within the corpora cavernosa and spongiosum. Release of NO activates a signaling pathway that results in relaxation of the smooth muscles that surround the penile arteries, causing them to dilate. This dilation increases the amount of blood that can enter the penis and induces the endothelial cells in the penile arterial walls to also secrete NO and perpetuate the vasodilation. The rapid increase in blood volume fills the erectile chambers, and the increased pressure of the filled chambers compresses the thin-walled penile venules, preventing venous drainage of the penis. The result of this increased blood flow to the penis and reduced blood return from the penis is erection. Depending on the flaccid dimensions of a penis, it can increase in size slightly or greatly during erection, with the average length of an erect penis measuring approximately 15 cm.

Note:
Disorders of the… Feature
Male Reproductive System
Erectile dysfunction (ED) is a condition in which a man has difficulty either initiating or maintaining an erection. The combined prevalence of minimal, moderate, and complete ED is approximately 40 percent in men at age 40, and reaches nearly 70 percent by 70 years of age. In addition to aging, ED is associated with diabetes, vascular disease, psychiatric disorders, prostate disorders, the use of some drugs such as certain antidepressants, and problems with the testes resulting in low testosterone concentrations. These physical and emotional conditions can lead to

interruptions in the vasodilation pathway and result in an inability to achieve an erection.

Recall that the release of NO induces relaxation of the smooth muscles that surround the penile arteries, leading to the vasodilation necessary to achieve an erection. To reverse the process of vasodilation, an enzyme called phosphodiesterase (PDE) degrades a key component of the NO signaling pathway called cGMP. There are several different forms of this enzyme, and PDE type 5 is the type of PDE found in the tissues of the penis. Scientists discovered that inhibiting PDE5 increases blood flow, and allows vasodilation of the penis to occur.

PDEs and the vasodilation signaling pathway are found in the vasculature in other parts of the body. In the 1990s, clinical trials of a PDE5 inhibitor called sildenafil were initiated to treat hypertension and angina pectoris (chest pain caused by poor blood flow through the heart). The trial showed that the drug was not effective at treating heart conditions, but many men experienced erection and priapism (erection lasting longer than 4 hours). Because of this, a clinical trial was started to investigate the ability of sildenafil to promote erections in men suffering from ED. In 1998, the FDA approved the drug, marketed as Viagra®. Since approval of the drug, sildenafil and similar PDE inhibitors now generate over a billion dollars a year in sales, and are reported to be effective in treating approximately 70 to 85 percent of cases of ED. Importantly, men with health problems—especially those with cardiac disease taking nitrates—should avoid Viagra or talk to their physician to find out if they are a candidate for the use of this drug, as deaths have been reported for at-risk users.

Testosterone

Testosterone, an androgen, is a steroid hormone produced by **Leydig cells**. The alternate term for Leydig cells, interstitial cells, reflects their location between the seminiferous tubules in the testes. In male embryos, testosterone is secreted by Leydig cells by the seventh week of development, with peak concentrations reached in the second trimester. This early release of testosterone results in the anatomical differentiation of the male sexual organs. In childhood, testosterone concentrations are low.

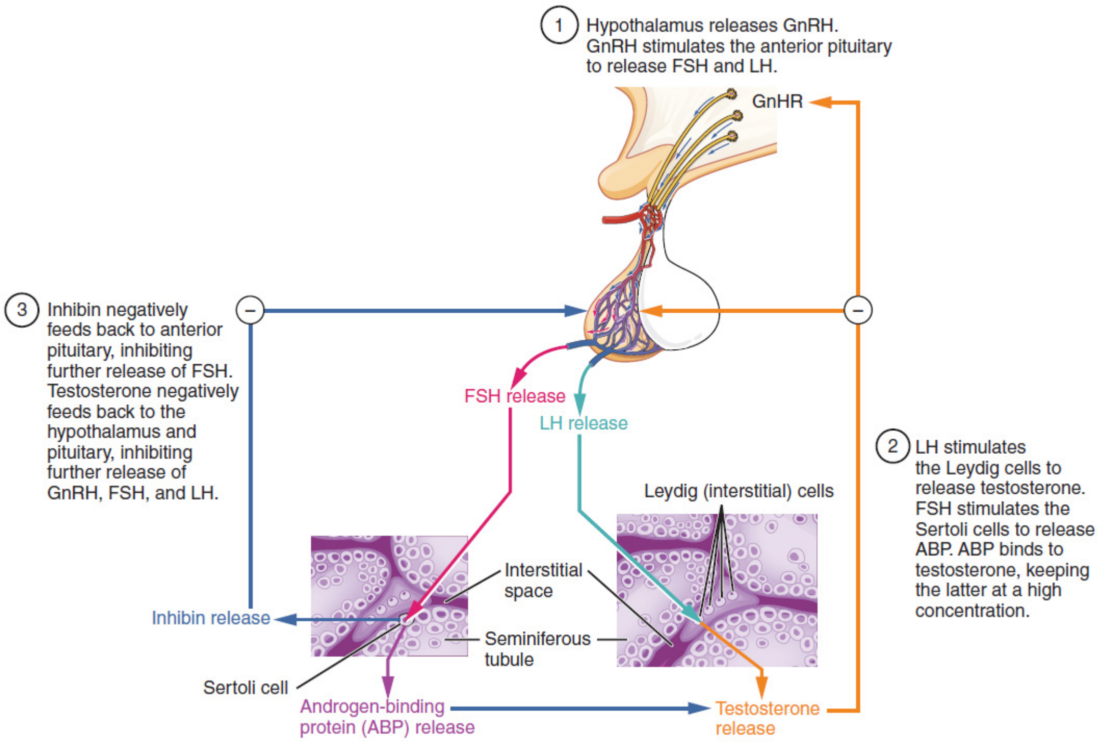
They increase during puberty, activating characteristic physical changes and initiating spermatogenesis.

Functions of Testosterone

The continued presence of testosterone is necessary to keep the male reproductive system working properly, and Leydig cells produce approximately 6 to 7 mg of testosterone per day. Testicular steroidogenesis (the manufacture of androgens, including testosterone) results in testosterone concentrations that are 100 times higher in the testes than in the circulation. Maintaining these normal concentrations of testosterone promotes spermatogenesis, whereas low levels of testosterone can lead to infertility. In addition to intratesticular secretion, testosterone is also released into the systemic circulation and plays an important role in muscle development, bone growth, the development of secondary sex characteristics, and maintaining libido (sex drive) in both males and females. In females, the ovaries secrete small amounts of testosterone, although most is converted to estradiol. A small amount of testosterone is also secreted by the adrenal glands in both sexes.

Control of Testosterone

The regulation of testosterone concentrations throughout the body is critical for male reproductive function. The intricate interplay between the endocrine system and the reproductive system is shown in [link].
Regulation of Testosterone Production



The hypothalamus and pituitary gland regulate the production of testosterone and the cells that assist in spermatogenesis. GnRH activates the anterior pituitary to produce LH and FSH, which in turn stimulate Leydig cells and Sertoli cells, respectively. The system is a negative feedback loop because the end products of the pathway, testosterone and inhibin, interact with the activity of GnRH to inhibit their own production.

The regulation of Leydig cell production of testosterone begins outside of the testes. The hypothalamus and the pituitary gland in the brain integrate external and internal signals to control testosterone synthesis and secretion. The regulation begins in the hypothalamus. Pulsatile release of a hormone called **gonadotropin-releasing hormone (GnRH)** from the hypothalamus stimulates the endocrine release of hormones from the pituitary gland. Binding of GnRH to its receptors on the anterior pituitary gland stimulates release of the two gonadotropins: luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These two hormones are critical for

reproductive function in both men and women. In men, FSH binds predominantly to the Sertoli cells within the seminiferous tubules to promote spermatogenesis. FSH also stimulates the Sertoli cells to produce hormones called inhibins, which function to inhibit FSH release from the pituitary, thus reducing testosterone secretion. These polypeptide hormones correlate directly with Sertoli cell function and sperm number; inhibin B can be used as a marker of spermatogenic activity. In men, LH binds to receptors on Leydig cells in the testes and upregulates the production of testosterone.

A negative feedback loop predominantly controls the synthesis and secretion of both FSH and LH. Low blood concentrations of testosterone stimulate the hypothalamic release of GnRH. GnRH then stimulates the anterior pituitary to secrete LH into the bloodstream. In the testis, LH binds to LH receptors on Leydig cells and stimulates the release of testosterone. When concentrations of testosterone in the blood reach a critical threshold, testosterone itself will bind to androgen receptors on both the hypothalamus and the anterior pituitary, inhibiting the synthesis and secretion of GnRH and LH, respectively. When the blood concentrations of testosterone once again decline, testosterone no longer interacts with the receptors to the same degree and GnRH and LH are once again secreted, stimulating more testosterone production. This same process occurs with FSH and inhibin to control spermatogenesis.

Note:
Aging and the… Feature
Male Reproductive System
Declines in Leydig cell activity can occur in men beginning at 40 to 50 years of age. The resulting reduction in circulating testosterone concentrations can lead to symptoms of andropause, also known as male menopause. While the reduction in sex steroids in men is akin to female menopause, there is no clear sign—such as a lack of a menstrual period—to denote the initiation of andropause. Instead, men report feelings of fatigue, reduced muscle mass, depression, anxiety, irritability, loss of libido, and insomnia. A reduction in spermatogenesis resulting in lowered

fertility is also reported, and sexual dysfunction can also be associated with andropausal symptoms.

Whereas some researchers believe that certain aspects of andropause are difficult to tease apart from aging in general, testosterone replacement is sometimes prescribed to alleviate some symptoms. Recent studies have shown a benefit from androgen replacement therapy on the new onset of depression in elderly men; however, other studies caution against testosterone replacement for long-term treatment of andropause symptoms, showing that high doses can sharply increase the risk of both heart disease and prostate cancer.

Chapter Review

Gametes are the reproductive cells that combine to form offspring. Organs called gonads produce the gametes, along with the hormones that regulate human reproduction. The male gametes are called sperm. Spermatogenesis, the production of sperm, occurs within the seminiferous tubules that make up most of the testis. The scrotum is the muscular sac that holds the testes outside of the body cavity.

Spermatogenesis begins with mitotic division of spermatogonia (stem cells) to produce primary spermatocytes that undergo the two divisions of meiosis to become secondary spermatocytes, then the haploid spermatids. During spermiogenesis, spermatids are transformed into spermatozoa (formed sperm). Upon release from the seminiferous tubules, sperm are moved to the epididymis where they continue to mature. During ejaculation, sperm exit the epididymis through the ductus deferens, a duct in the spermatic cord that leaves the scrotum. The ampulla of the ductus deferens meets the seminal vesicle, a gland that contributes fructose and proteins, at the ejaculatory duct. The fluid continues through the prostatic urethra, where secretions from the prostate are added to form semen. These secretions help the sperm to travel through the urethra and into the female reproductive tract. Secretions from the bulbourethral glands protect sperm and cleanse and lubricate the penile (spongy) urethra.

The penis is the male organ of copulation. Columns of erectile tissue called the corpora cavernosa and corpus spongiosum fill with blood when sexual arousal activates vasodilatation in the blood vessels of the penis. Testosterone regulates and maintains the sex organs and sex drive, and induces the physical changes of puberty. Interplay between the testes and the endocrine system precisely control the production of testosterone with a negative feedback loop.

Interactive Link Questions

Exercise:

Problem:

Watch this video to learn about vasectomy. As described in this video, a vasectomy is a procedure in which a small section of the ductus (vas) deferens is removed from the scrotum. This interrupts the path taken by sperm through the ductus deferens. If sperm do not exit through the vas, either because the man has had a vasectomy or has not ejaculated, in what region of the testis do they remain?

Solution:

Sperm remain in the epididymis until they degenerate.

Exercise:

Problem:

Watch this video to explore the structures of the male reproductive system and the path of sperm that starts in the testes and ends as the sperm leave the penis through the urethra. Where are sperm deposited after they leave the ejaculatory duct?

Solution:

Sperm enter the prostate.

Review Questions

Exercise:

Problem: What are male gametes called?

a. ova
b. sperm
c. testes
d. testosterone

Solution:

b

Exercise:

Problem: Leydig cells _________.

a. secrete testosterone
b. activate the sperm flagellum
c. support spermatogenesis
d. secrete seminal fluid

Solution:

a

Exercise:

Problem:

Which hypothalamic hormone contributes to the regulation of the male reproductive system?

a. luteinizing hormone
b. gonadotropin-releasing hormone

c. follicle-stimulating hormone
d. androgens

Solution:

b

Exercise:

Problem: What is the function of the epididymis?

a. sperm maturation and storage
b. produces the bulk of seminal fluid
c. provides nitric oxide needed for erections
d. spermatogenesis

Solution:

a

Exercise:

Problem: Spermatogenesis takes place in the ________.

a. prostate gland
b. glans penis
c. seminiferous tubules
d. ejaculatory duct

Solution:

c

Critical Thinking Questions

Exercise:

Problem:

Briefly explain why mature gametes carry only one set of chromosomes.

Solution:

A single gamete must combine with a gamete from an individual of the opposite sex to produce a fertilized egg, which has a complete set of chromosomes and is the first cell of a new individual.

Exercise:

Problem:

What special features are evident in sperm cells but not in somatic cells, and how do these specializations function?

Solution:

Unlike somatic cells, sperm are haploid. They also have very little cytoplasm. They have a head with a compact nucleus covered by an acrosome filled with enzymes, and a mid-piece filled with mitochondria that power their movement. They are motile because of their tail, a structure containing a flagellum, which is specialized for movement.

Exercise:

Problem:

What do each of the three male accessory glands contribute to the semen?

Solution:

The three accessory glands make the following contributions to semen: the seminal vesicle contributes about 60 percent of the semen volume, with fluid that contains large amounts of fructose to power the

movement of sperm; the prostate gland contributes substances critical to sperm maturation; and the bulbourethral glands contribute a thick fluid that lubricates the ends of the urethra and the vagina and helps to clean urine residues from the urethra.

Exercise:

Problem: Describe how penile erection occurs.

Solution:

During sexual arousal, nitric oxide (NO) is released from nerve endings near blood vessels within the corpora cavernosa and corpus spongiosum. The release of NO activates a signaling pathway that results in relaxation of the smooth muscles that surround the penile arteries, causing them to dilate. This dilation increases the amount of blood that can enter the penis, and induces the endothelial cells in the penile arterial walls to secrete NO, perpetuating the vasodilation. The rapid increase in blood volume fills the erectile chambers, and the increased pressure of the filled chambers compresses the thin-walled penile venules, preventing venous drainage of the penis. An erection is the result of this increased blood flow to the penis and reduced blood return from the penis.

Exercise:

Problem:

While anabolic steroids (synthetic testosterone) bulk up muscles, they can also affect testosterone production in the testis. Using what you know about negative feedback, describe what would happen to testosterone production in the testis if a male takes large amounts of synthetic testosterone.

Solution:

Testosterone production by the body would be reduced if a male were taking anabolic steroids. This is because the hypothalamus responds to rising testosterone levels by reducing its secretion of GnRH, which

would in turn reduce the anterior pituitary’s release of LH, finally reducing the manufacture of testosterone in the testes.

Glossary

blood–testis barrier
: tight junctions between Sertoli cells that prevent bloodborne pathogens from gaining access to later stages of spermatogenesis and prevent the potential for an autoimmune reaction to haploid sperm

bulbourethral glands
: (also, Cowper’s glands) glands that secrete a lubricating mucus that cleans and lubricates the urethra prior to and during ejaculation

corpus cavernosum
: either of two columns of erectile tissue in the penis that fill with blood during an erection

corpus spongiosum
: (plural = corpora cavernosa) column of erectile tissue in the penis that fills with blood during an erection and surrounds the penile urethra on the ventral portion of the penis

ductus deferens
: (also, vas deferens) duct that transports sperm from the epididymis through the spermatic cord and into the ejaculatory duct; also referred as the vas deferens

ejaculatory duct
: duct that connects the ampulla of the ductus deferens with the duct of the seminal vesicle at the prostatic urethra

epididymis
: (plural = epididymides) coiled tubular structure in which sperm start to mature and are stored until ejaculation

gamete

haploid reproductive cell that contributes genetic material to form an offspring

glans penis
: bulbous end of the penis that contains a large number of nerve endings

gonadotropin-releasing hormone (GnRH)
: hormone released by the hypothalamus that regulates the production of follicle-stimulating hormone and luteinizing hormone from the pituitary gland

gonads
: reproductive organs (testes in men and ovaries in women) that produce gametes and reproductive hormones

inguinal canal
: opening in abdominal wall that connects the testes to the abdominal cavity

Leydig cells
: cells between the seminiferous tubules of the testes that produce testosterone; a type of interstitial cell

penis
: male organ of copulation

prepuce
: (also, foreskin) flap of skin that forms a collar around, and thus protects and lubricates, the glans penis; also referred as the foreskin

prostate gland
: doughnut-shaped gland at the base of the bladder surrounding the urethra and contributing fluid to semen during ejaculation

scrotum
: external pouch of skin and muscle that houses the testes

semen

ejaculatory fluid composed of sperm and secretions from the seminal vesicles, prostate, and bulbourethral glands

seminal vesicle
: gland that produces seminal fluid, which contributes to semen

seminiferous tubules
: tube structures within the testes where spermatogenesis occurs

Sertoli cells
: cells that support germ cells through the process of spermatogenesis; a type of sustentacular cell

sperm
: (also, spermatozoon) male gamete

spermatic cord
: bundle of nerves and blood vessels that supplies the testes; contains ductus deferens

spermatid
: immature sperm cells produced by meiosis II of secondary spermatocytes

spermatocyte
: cell that results from the division of spermatogonium and undergoes meiosis I and meiosis II to form spermatids

spermatogenesis
: formation of new sperm, occurs in the seminiferous tubules of the testes

spermatogonia
: (singular = spermatogonium) diploid precursor cells that become sperm

spermiogenesis
: transformation of spermatids to spermatozoa during spermatogenesis

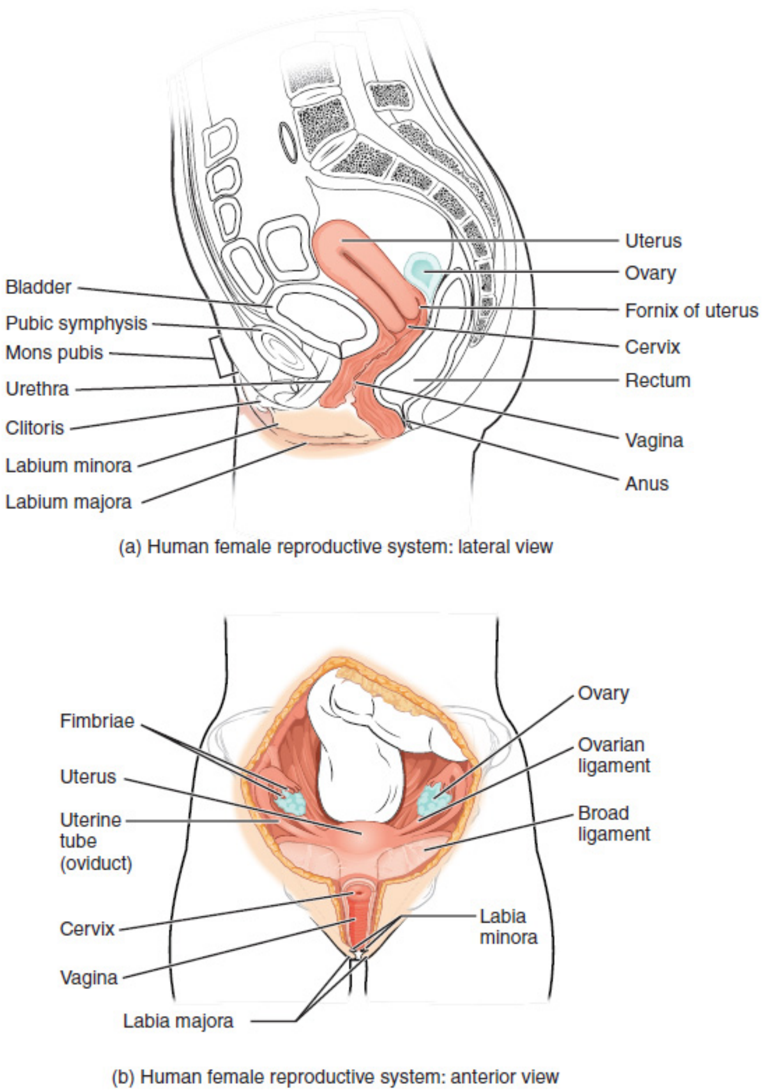
testes

(singular = testis) male gonads

Anatomy and Physiology of the Female Reproductive System
By the end of this section, you will be able to:

- Describe the structure and function of the organs of the female reproductive system
- List the steps of oogenesis
- Describe the hormonal changes that occur during the ovarian and menstrual cycles
- Trace the path of an oocyte from ovary to fertilization

The female reproductive system functions to produce gametes and reproductive hormones, just like the male reproductive system; however, it also has the additional task of supporting the developing fetus and delivering it to the outside world. Unlike its male counterpart, the female reproductive system is located primarily inside the pelvic cavity ([link]). Recall that the ovaries are the female gonads. The gamete they produce is called an **oocyte**. We'll discuss the production of oocytes in detail shortly. First, let's look at some of the structures of the female reproductive system.
Female Reproductive System



The major organs of the female reproductive system are located inside the pelvic cavity.

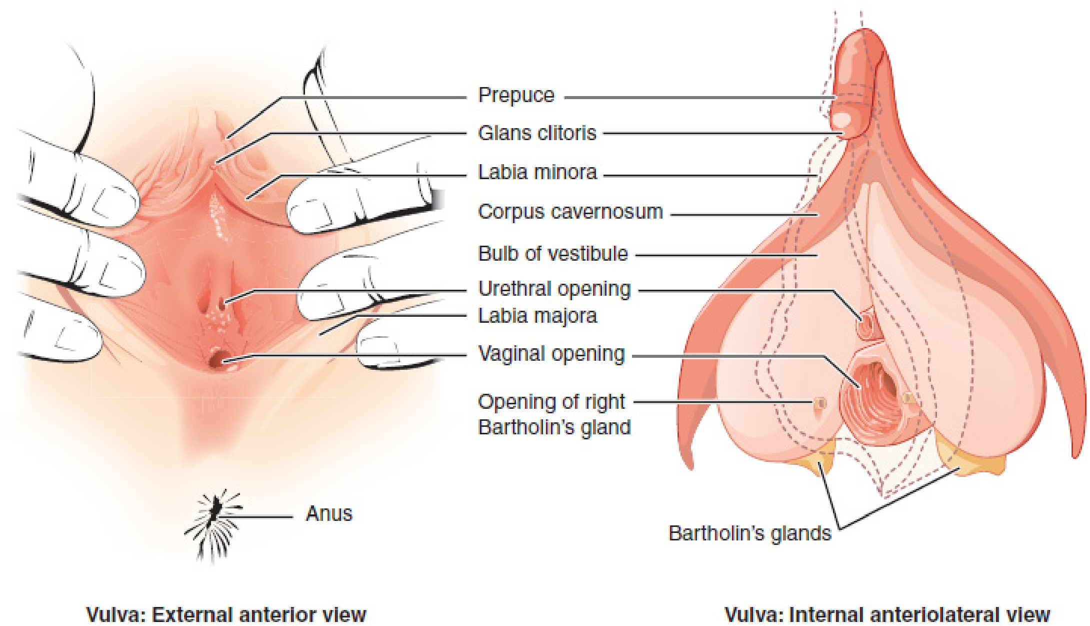
External Female Genitals

The external female reproductive structures are referred to collectively as the **vulva** ([link]). The **mons pubis** is a pad of fat that is located at the anterior, over the pubic bone. After puberty, it becomes covered in pubic hair. The **labia majora** (labia = “lips”; majora = “larger”) are folds of hair-

covered skin that begin just posterior to the mons pubis. The thinner and more pigmented **labia minora** (labia = “lips”; minora = “smaller”) extend medial to the labia majora. Although they naturally vary in shape and size from woman to woman, the labia minora serve to protect the female urethra and the entrance to the female reproductive tract.

The superior, anterior portions of the labia minora come together to encircle the **clitoris** (or glans clitoris), an organ that originates from the same cells as the glans penis and has abundant nerves that make it important in sexual sensation and orgasm. The **hymen** is a thin membrane that sometimes partially covers the entrance to the vagina. An intact hymen cannot be used as an indication of “virginity”; even at birth, this is only a partial membrane, as menstrual fluid and other secretions must be able to exit the body, regardless of penile–vaginal intercourse. The vaginal opening is located between the opening of the urethra and the anus. It is flanked by outlets to the **Bartholin’s glands** (or greater vestibular glands).

The Vulva



The external female genitalia are referred to collectively as the vulva.

Vagina

The **vagina**, shown at the bottom of [link] and [link], is a muscular canal (approximately 10 cm long) that serves as the entrance to the reproductive tract. It also serves as the exit from the uterus during menses and childbirth. The outer walls of the anterior and posterior vagina are formed into longitudinal columns, or ridges, and the superior portion of the vagina—called the fornix—meets the protruding uterine cervix. The walls of the vagina are lined with an outer, fibrous adventitia; a middle layer of smooth muscle; and an inner mucous membrane with transverse folds called **rugae**. Together, the middle and inner layers allow the expansion of the vagina to accommodate intercourse and childbirth. The thin, perforated hymen can partially surround the opening to the vaginal orifice. The hymen can be ruptured with strenuous physical exercise, penile–vaginal intercourse, and childbirth. The Bartholin's glands and the lesser vestibular glands (located near the clitoris) secrete mucus, which keeps the vestibular area moist.

The vagina is home to a normal population of microorganisms that help to protect against infection by pathogenic bacteria, yeast, or other organisms that can enter the vagina. In a healthy woman, the most predominant type of vaginal bacteria is from the genus *Lactobacillus*. This family of beneficial bacterial flora secretes lactic acid, and thus protects the vagina by maintaining an acidic pH (below 4.5). Potential pathogens are less likely to survive in these acidic conditions. Lactic acid, in combination with other vaginal secretions, makes the vagina a self-cleansing organ. However, douching—or washing out the vagina with fluid—can disrupt the normal balance of healthy microorganisms, and actually increase a woman's risk for infections and irritation. Indeed, the American College of Obstetricians and Gynecologists recommend that women do not douche, and that they allow the vagina to maintain its normal healthy population of protective microbial flora.

Ovaries

The **ovaries** are the female gonads (see [link]). Paired ovals, they are each about 2 to 3 cm in length, about the size of an almond. The ovaries are located within the pelvic cavity, and are supported by the mesovarium, an

extension of the peritoneum that connects the ovaries to the **broad ligament**. Extending from the mesovarium itself is the suspensory ligament that contains the ovarian blood and lymph vessels. Finally, the ovary itself is attached to the uterus via the ovarian ligament.

The ovary comprises an outer covering of cuboidal epithelium called the ovarian surface epithelium that is superficial to a dense connective tissue covering called the tunica albuginea. Beneath the tunica albuginea is the cortex, or outer portion, of the organ. The cortex is composed of a tissue framework called the ovarian stroma that forms the bulk of the adult ovary. Oocytes develop within the outer layer of this stroma, each surrounded by supporting cells. This grouping of an oocyte and its supporting cells is called a **follicle**. The growth and development of ovarian follicles will be described shortly. Beneath the cortex lies the inner ovarian medulla, the site of blood vessels, lymph vessels, and the nerves of the ovary. You will learn more about the overall anatomy of the female reproductive system at the end of this section.

The Ovarian Cycle

The **ovarian cycle** is a set of predictable changes in a female’s oocytes and ovarian follicles. During a woman’s reproductive years, it is a roughly 28-day cycle that can be correlated with, but is not the same as, the menstrual cycle (discussed shortly). The cycle includes two interrelated processes: oogenesis (the production of female gametes) and folliculogenesis (the growth and development of ovarian follicles).

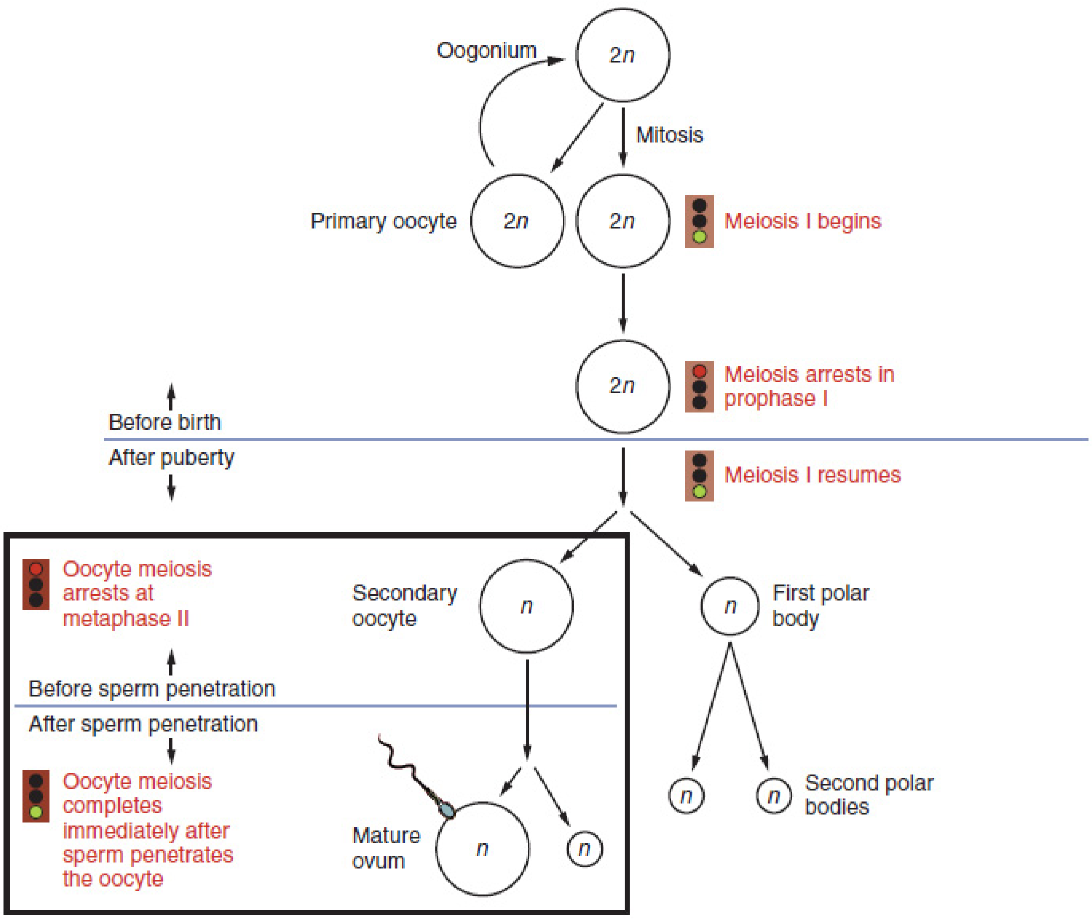
Oogenesis

Gametogenesis in females is called **oogenesis**. The process begins with the ovarian stem cells, or **oogonia** ([link]). Oogonia are formed during fetal development, and divide via mitosis, much like spermatogonia in the testis. Unlike spermatogonia, however, oogonia form primary oocytes in the fetal ovary prior to birth. These primary oocytes are then arrested in this stage of meiosis I, only to resume it years later, beginning at puberty and continuing

until the woman is near menopause (the cessation of a woman's reproductive functions). The number of primary oocytes present in the ovaries declines from one to two million in an infant, to approximately 400,000 at puberty, to zero by the end of menopause.

The initiation of **ovulation**—the release of an oocyte from the ovary—marks the transition from puberty into reproductive maturity for women. From then on, throughout a woman's reproductive years, ovulation occurs approximately once every 28 days. Just prior to ovulation, a surge of luteinizing hormone triggers the resumption of meiosis in a primary oocyte. This initiates the transition from primary to secondary oocyte. However, as you can see in [link], this cell division does not result in two identical cells. Instead, the cytoplasm is divided unequally, and one daughter cell is much larger than the other. This larger cell, the secondary oocyte, eventually leaves the ovary during ovulation. The smaller cell, called the first **polar body**, may or may not complete meiosis and produce second polar bodies; in either case, it eventually disintegrates. Therefore, even though oogenesis produces up to four cells, only one survives.

Oogenesis



The unequal cell division of oogenesis produces one to three polar bodies that later degrade, as well as a single haploid ovum, which is produced only if there is penetration of the secondary oocyte by a sperm cell.

How does the diploid secondary oocyte become an **ovum**—the haploid female gamete? Meiosis of a secondary oocyte is completed only if a sperm succeeds in penetrating its barriers. Meiosis II then resumes, producing one haploid ovum that, at the instant of fertilization by a (haploid) sperm, becomes the first diploid cell of the new offspring (a zygote). Thus, the ovum can be thought of as a brief, transitional, haploid stage between the diploid oocyte and diploid zygote.

The larger amount of cytoplasm contained in the female gamete is used to supply the developing zygote with nutrients during the period between fertilization and implantation into the uterus. Interestingly, sperm contribute only DNA at fertilization —not cytoplasm. Therefore, the cytoplasm and all of the cytoplasmic organelles in the developing embryo are of maternal origin. This includes mitochondria, which contain their own DNA. Scientific research in the 1980s determined that mitochondrial DNA was maternally inherited, meaning that you can trace your mitochondrial DNA directly to your mother, her mother, and so on back through your female ancestors.

Note:

Everyday Connections Feature

Mapping Human History with Mitochondrial DNA

When we talk about human DNA, we're usually referring to nuclear DNA; that is, the DNA coiled into chromosomal bundles in the nucleus of our cells. We inherit half of our nuclear DNA from our father, and half from our mother. However, mitochondrial DNA (mtDNA) comes only from the mitochondria in the cytoplasm of the fat ovum we inherit from our mother. She received her mtDNA from her mother, who got it from her mother, and so on. Each of our cells contains approximately 1700 mitochondria, with each mitochondrion packed with mtDNA containing approximately 37 genes.

Mutations (changes) in mtDNA occur spontaneously in a somewhat organized pattern at regular intervals in human history. By analyzing these mutational relationships, researchers have been able to determine that we can all trace our ancestry back to one woman who lived in Africa about 200,000 years ago. Scientists have given this woman the biblical name Eve, although she is not, of course, the first *Homo sapiens* female. More precisely, she is our most recent common ancestor through matrilineal descent.

This doesn't mean that everyone's mtDNA today looks exactly like that of our ancestral Eve. Because of the spontaneous mutations in mtDNA that have occurred over the centuries, researchers can map different "branches" off of the "main trunk" of our mtDNA family tree. Your mtDNA might

have a pattern of mutations that aligns more closely with one branch, and your neighbor's may align with another branch. Still, all branches eventually lead back to Eve.

But what happened to the mtDNA of all of the other *Homo sapiens* females who were living at the time of Eve? Researchers explain that, over the centuries, their female descendants died childless or with only male children, and thus, their maternal line—and its mtDNA—ended.

Folliculogenesis

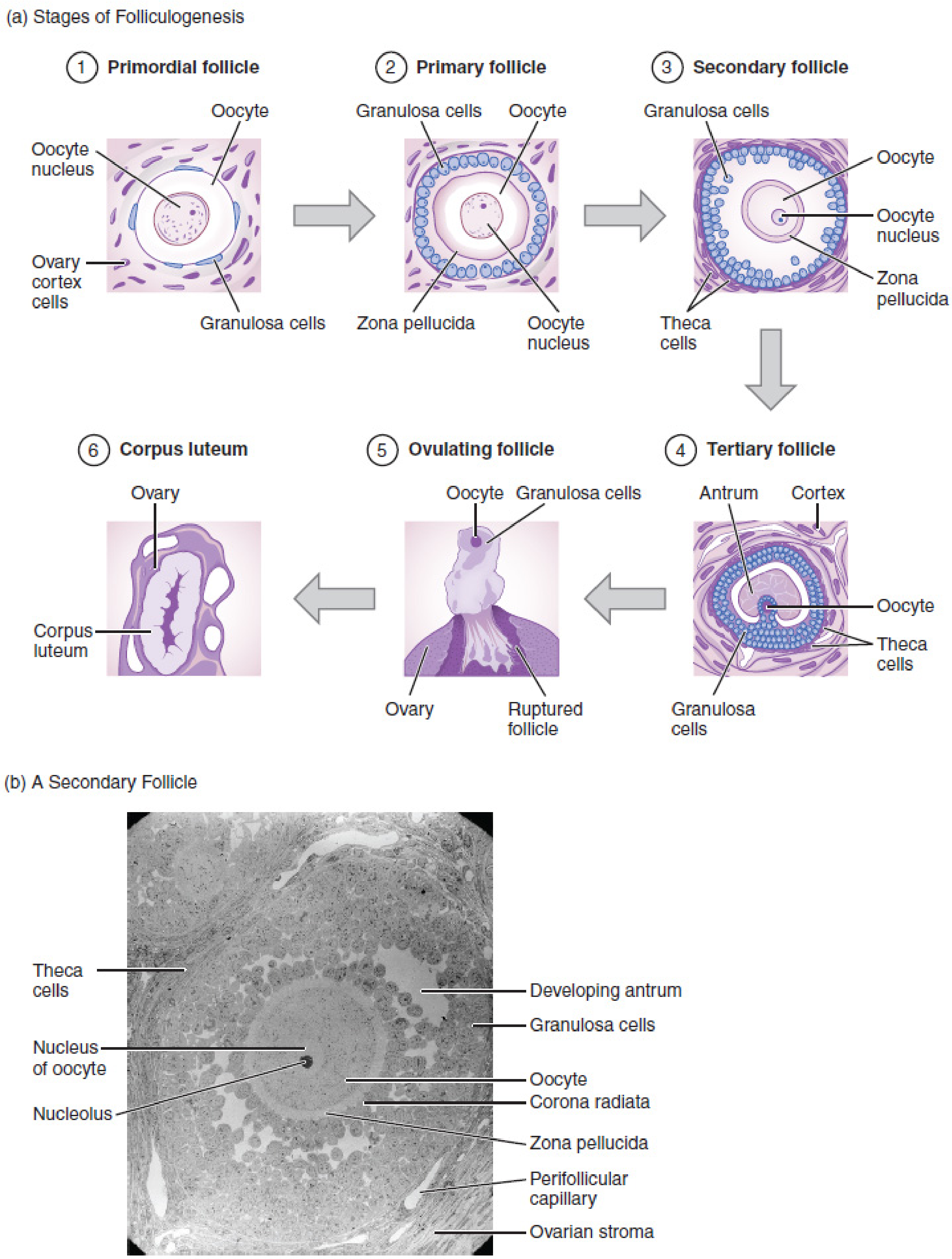
Again, ovarian follicles are oocytes and their supporting cells. They grow and develop in a process called **folliculogenesis**, which typically leads to ovulation of one follicle approximately every 28 days, along with death to multiple other follicles. The death of ovarian follicles is called atresia, and can occur at any point during follicular development. Recall that, a female infant at birth will have one to two million oocytes within her ovarian follicles, and that this number declines throughout life until menopause, when no follicles remain. As you'll see next, follicles progress from primordial, to primary, to secondary and tertiary stages prior to ovulation—with the oocyte inside the follicle remaining as a primary oocyte until right before ovulation.

Folliculogenesis begins with follicles in a resting state. These small **primordial follicles** are present in newborn females and are the prevailing follicle type in the adult ovary ([link]). Primordial follicles have only a single flat layer of support cells, called **granulosa cells**, that surround the oocyte, and they can stay in this resting state for years—some until right before menopause.

After puberty, a few primordial follicles will respond to a recruitment signal each day, and will join a pool of immature growing follicles called **primary follicles**. Primary follicles start with a single layer of granulosa cells, but the granulosa cells then become active and transition from a flat or squamous shape to a rounded, cuboidal shape as they increase in size and proliferate. As the granulosa cells divide, the follicles—now called **secondary follicles** (see [link])—increase in diameter, adding a new outer

layer of connective tissue, blood vessels, and **theca cells**—cells that work with the granulosa cells to produce estrogens.

Within the growing secondary follicle, the primary oocyte now secretes a thin acellular membrane called the zona pellucida that will play a critical role in fertilization. A thick fluid, called follicular fluid, that has formed between the granulosa cells also begins to collect into one large pool, or **antrum**. Follicles in which the antrum has become large and fully formed are considered **tertiary follicles** (or antral follicles). Several follicles reach the tertiary stage at the same time, and most of these will undergo atresia. The one that does not die will continue to grow and develop until ovulation, when it will expel its secondary oocyte surrounded by several layers of granulosa cells from the ovary. Keep in mind that most follicles don’t make it to this point. In fact, roughly 99 percent of the follicles in the ovary will undergo atresia, which can occur at any stage of folliculogenesis.
Folliculogenesis



(a) The maturation of a follicle is shown in a clockwise direction proceeding from the primordial follicles. FSH stimulates the growth of a tertiary follicle, and LH stimulates the production of estrogen by granulosa and theca cells. Once the follicle is mature, it ruptures and releases the oocyte. Cells

remaining in the follicle then develop into the corpus luteum. (b) In this electron micrograph of a secondary follicle, the oocyte, theca cells (thecae folliculi), and developing antrum are clearly visible. EM × 1100. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Hormonal Control of the Ovarian Cycle

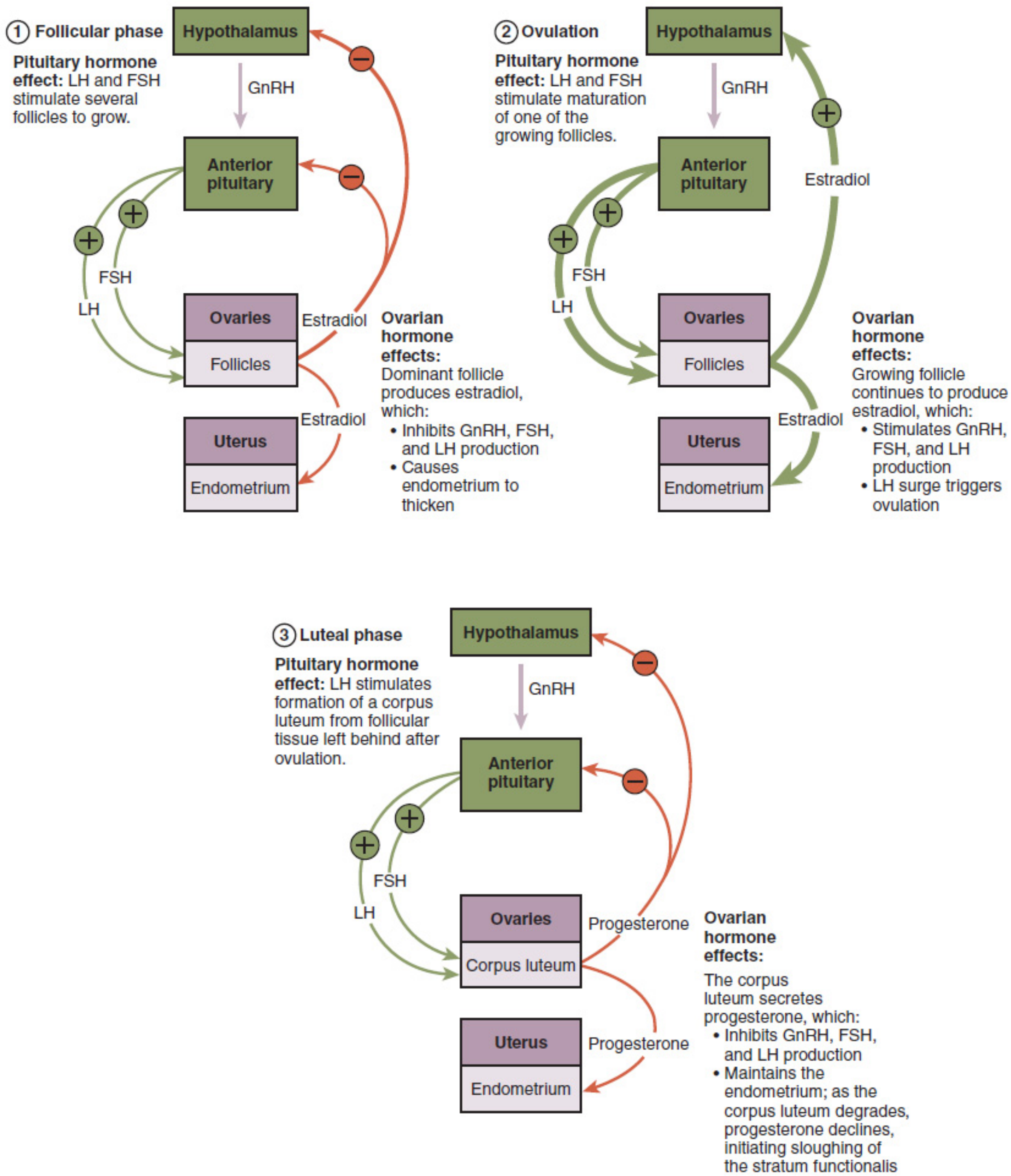
The process of development that we have just described, from primordial follicle to early tertiary follicle, takes approximately two months in humans. The final stages of development of a small cohort of tertiary follicles, ending with ovulation of a secondary oocyte, occur over a course of approximately 28 days. These changes are regulated by many of the same hormones that regulate the male reproductive system, including GnRH, LH, and FSH.

As in men, the hypothalamus produces GnRH, a hormone that signals the anterior pituitary gland to produce the gonadotropins FSH and LH ([link]). These gonadotropins leave the pituitary and travel through the bloodstream to the ovaries, where they bind to receptors on the granulosa and theca cells of the follicles. FSH stimulates the follicles to grow (hence its name of follicle-stimulating hormone), and the five or six tertiary follicles expand in diameter. The release of LH also stimulates the granulosa and theca cells of the follicles to produce the sex steroid hormone estradiol, a type of estrogen. This phase of the ovarian cycle, when the tertiary follicles are growing and secreting estrogen, is known as the follicular phase.

The more granulosa and theca cells a follicle has (that is, the larger and more developed it is), the more estrogen it will produce in response to LH stimulation. As a result of these large follicles producing large amounts of estrogen, systemic plasma estrogen concentrations increase. Following a classic negative feedback loop, the high concentrations of estrogen will stimulate the hypothalamus and pituitary to reduce the production of GnRH, LH, and FSH. Because the large tertiary follicles require FSH to grow and

survive at this point, this decline in FSH caused by negative feedback leads most of them to die (atresia). Typically only one follicle, now called the dominant follicle, will survive this reduction in FSH, and this follicle will be the one that releases an oocyte. Scientists have studied many factors that lead to a particular follicle becoming dominant: size, the number of granulosa cells, and the number of FSH receptors on those granulosa cells all contribute to a follicle becoming the one surviving dominant follicle.

Hormonal Regulation of Ovulation



The hypothalamus and pituitary gland regulate the ovarian cycle and ovulation. GnRH activates the anterior pituitary to produce LH and FSH, which stimulate the production of estrogen and progesterone by the ovaries.

When only the one dominant follicle remains in the ovary, it again begins to secrete estrogen. It produces more estrogen than all of the developing follicles did together before the negative feedback occurred. It produces so much estrogen that the normal negative feedback doesn’t occur. Instead, these extremely high concentrations of systemic plasma estrogen trigger a regulatory switch in the anterior pituitary that responds by secreting large amounts of LH and FSH into the bloodstream (see [link]). The positive feedback loop by which more estrogen triggers release of more LH and FSH only occurs at this point in the cycle.

It is this large burst of LH (called the LH surge) that leads to ovulation of the dominant follicle. The LH surge induces many changes in the dominant follicle, including stimulating the resumption of meiosis of the primary oocyte to a secondary oocyte. As noted earlier, the polar body that results from unequal cell division simply degrades. The LH surge also triggers proteases (enzymes that cleave proteins) to break down structural proteins in the ovary wall on the surface of the bulging dominant follicle. This degradation of the wall, combined with pressure from the large, fluid-filled antrum, results in the expulsion of the oocyte surrounded by granulosa cells into the peritoneal cavity. This release is ovulation.

In the next section, you will follow the ovulated oocyte as it travels toward the uterus, but there is one more important event that occurs in the ovarian cycle. The surge of LH also stimulates a change in the granulosa and theca cells that remain in the follicle after the oocyte has been ovulated. This change is called luteinization (recall that the full name of LH is luteinizing hormone), and it transforms the collapsed follicle into a new endocrine structure called the **corpus luteum**, a term meaning “yellowish body” (see [link]). Instead of estrogen, the luteinized granulosa and theca cells of the corpus luteum begin to produce large amounts of the sex steroid hormone

progesterone, a hormone that is critical for the establishment and maintenance of pregnancy. Progesterone triggers negative feedback at the hypothalamus and pituitary, which keeps GnRH, LH, and FSH secretions low, so no new dominant follicles develop at this time.

The post-ovulatory phase of progesterone secretion is known as the luteal phase of the ovarian cycle. If pregnancy does not occur within 10 to 12 days, the corpus luteum will stop secreting progesterone and degrade into the **corpus albicans**, a nonfunctional “whitish body” that will disintegrate in the ovary over a period of several months. During this time of reduced progesterone secretion, FSH and LH are once again stimulated, and the follicular phase begins again with a new cohort of early tertiary follicles beginning to grow and secrete estrogen.

The Uterine Tubes

The **uterine tubes** (also called fallopian tubes or oviducts) serve as the conduit of the oocyte from the ovary to the uterus ([link]). Each of the two uterine tubes is close to, but not directly connected to, the ovary and divided into sections. The **isthmus** is the narrow medial end of each uterine tube that is connected to the uterus. The wide distal **infundibulum** flares out with slender, finger-like projections called **fimbriae**. The middle region of the tube, called the **ampulla**, is where fertilization often occurs. The uterine tubes also have three layers: an outer serosa, a middle smooth muscle layer, and an inner mucosal layer. In addition to its mucus-secreting cells, the inner mucosa contains ciliated cells that beat in the direction of the uterus, producing a current that will be critical to move the oocyte.

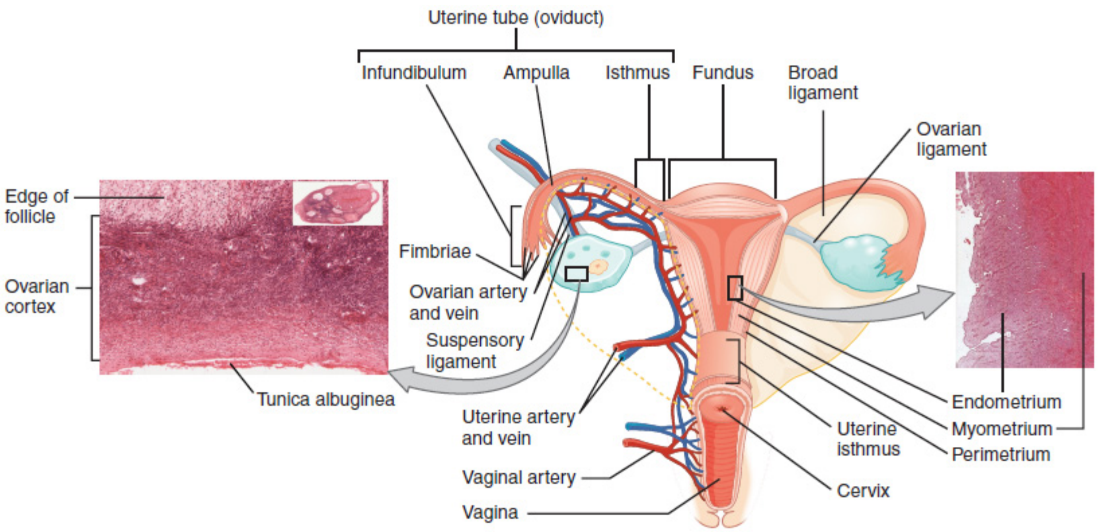
Following ovulation, the secondary oocyte surrounded by a few granulosa cells is released into the peritoneal cavity. The nearby uterine tube, either left or right, receives the oocyte. Unlike sperm, oocytes lack flagella, and therefore cannot move on their own. So how do they travel into the uterine tube and toward the uterus? High concentrations of estrogen that occur around the time of ovulation induce contractions of the smooth muscle along the length of the uterine tube. These contractions occur every 4 to 8 seconds, and the result is a coordinated movement that sweeps the surface of the ovary and the pelvic cavity. Current flowing toward the uterus is

generated by coordinated beating of the cilia that line the outside and lumen of the length of the uterine tube. These cilia beat more strongly in response to the high estrogen concentrations that occur around the time of ovulation. As a result of these mechanisms, the oocyte–granulosa cell complex is pulled into the interior of the tube. Once inside, the muscular contractions and beating cilia move the oocyte slowly toward the uterus. When fertilization does occur, sperm typically meet the egg while it is still moving through the ampulla.

Note:
Interactive Link

Watch this video to observe ovulation and its initiation in response to the release of FSH and LH from the pituitary gland. What specialized structures help guide the oocyte from the ovary into the uterine tube?

If the oocyte is successfully fertilized, the resulting zygote will begin to divide into two cells, then four, and so on, as it makes its way through the uterine tube and into the uterus. There, it will implant and continue to grow. If the egg is not fertilized, it will simply degrade—either in the uterine tube or in the uterus, where it may be shed with the next menstrual period.
Ovaries, Uterine Tubes, and Uterus



This anterior view shows the relationship of the ovaries, uterine tubes (oviducts), and uterus. Sperm enter through the vagina, and fertilization of an ovulated oocyte usually occurs in the distal uterine tube. From left to right, LM × 400, LM × 20. (Micrographs provided by the Regents of University of Michigan Medical School © 2012)

The open-ended structure of the uterine tubes can have significant health consequences if bacteria or other contagions enter through the vagina and move through the uterus, into the tubes, and then into the pelvic cavity. If this is left unchecked, a bacterial infection (sepsis) could quickly become life-threatening. The spread of an infection in this manner is of special concern when unskilled practitioners perform abortions in non-sterile conditions. Sepsis is also associated with sexually transmitted bacterial infections, especially gonorrhea and chlamydia. These increase a woman's risk for pelvic inflammatory disease (PID), infection of the uterine tubes or other reproductive organs. Even when resolved, PID can leave scar tissue in the tubes, leading to infertility.

Note:
Interactive Link

Watch this series of videos to look at the movement of the oocyte through the ovary. The cilia in the uterine tube promote movement of the oocyte. What would likely occur if the cilia were paralyzed at the time of ovulation?

The Uterus and Cervix

The **uterus** is the muscular organ that nourishes and supports the growing embryo (see [link]). Its average size is approximately 5 cm wide by 7 cm long (approximately 2 in by 3 in) when a female is not pregnant. It has three sections. The portion of the uterus superior to the opening of the uterine tubes is called the **fundus**. The middle section of the uterus is called the **body of uterus** (or corpus). The **cervix** is the narrow inferior portion of the uterus that projects into the vagina. The cervix produces mucus secretions that become thin and stringy under the influence of high systemic plasma estrogen concentrations, and these secretions can facilitate sperm movement through the reproductive tract.

Several ligaments maintain the position of the uterus within the abdominopelvic cavity. The broad ligament is a fold of peritoneum that serves as a primary support for the uterus, extending laterally from both sides of the uterus and attaching it to the pelvic wall. The round ligament attaches to the uterus near the uterine tubes, and extends to the labia majora. Finally, the uterosacral ligament stabilizes the uterus posteriorly by its connection from the cervix to the pelvic wall.

The wall of the uterus is made up of three layers. The most superficial layer is the serous membrane, or **perimetrium**, which consists of epithelial tissue that covers the exterior portion of the uterus. The middle layer, or

myometrium, is a thick layer of smooth muscle responsible for uterine contractions. Most of the uterus is myometrial tissue, and the muscle fibers run horizontally, vertically, and diagonally, allowing the powerful contractions that occur during labor and the less powerful contractions (or cramps) that help to expel menstrual blood during a woman's period. Anteriorly directed myometrial contractions also occur near the time of ovulation, and are thought to possibly facilitate the transport of sperm through the female reproductive tract.

The innermost layer of the uterus is called the **endometrium**. The endometrium contains a connective tissue lining, the lamina propria, which is covered by epithelial tissue that lines the lumen. Structurally, the endometrium consists of two layers: the stratum basalis and the stratum functionalis (the basal and functional layers). The stratum basalis layer is part of the lamina propria and is adjacent to the myometrium; this layer does not shed during menses. In contrast, the thicker stratum functionalis layer contains the glandular portion of the lamina propria and the endothelial tissue that lines the uterine lumen. It is the stratum functionalis that grows and thickens in response to increased levels of estrogen and progesterone. In the luteal phase of the menstrual cycle, special branches off of the uterine artery called spiral arteries supply the thickened stratum functionalis. This inner functional layer provides the proper site of implantation for the fertilized egg, and—should fertilization not occur—it is only the stratum functionalis layer of the endometrium that sheds during menstruation.

Recall that during the follicular phase of the ovarian cycle, the tertiary follicles are growing and secreting estrogen. At the same time, the stratum functionalis of the endometrium is thickening to prepare for a potential implantation. The post-ovulatory increase in progesterone, which characterizes the luteal phase, is key for maintaining a thick stratum functionalis. As long as a functional corpus luteum is present in the ovary, the endometrial lining is prepared for implantation. Indeed, if an embryo implants, signals are sent to the corpus luteum to continue secreting progesterone to maintain the endometrium, and thus maintain the pregnancy. If an embryo does not implant, no signal is sent to the corpus luteum and it degrades, ceasing progesterone production and ending the

luteal phase. Without progesterone, the endometrium thins and, under the influence of prostaglandins, the spiral arteries of the endometrium constrict and rupture, preventing oxygenated blood from reaching the endometrial tissue. As a result, endometrial tissue dies and blood, pieces of the endometrial tissue, and white blood cells are shed through the vagina during menstruation, or the **menses**. The first menses after puberty, called **menarche**, can occur either before or after the first ovulation.

The Menstrual Cycle

Now that we have discussed the maturation of the cohort of tertiary follicles in the ovary, the build-up and then shedding of the endometrial lining in the uterus, and the function of the uterine tubes and vagina, we can put everything together to talk about the three phases of the **menstrual cycle**—the series of changes in which the uterine lining is shed, rebuilds, and prepares for implantation.

The timing of the menstrual cycle starts with the first day of menses, referred to as day one of a woman’s period. Cycle length is determined by counting the days between the onset of bleeding in two subsequent cycles. Because the average length of a woman’s menstrual cycle is 28 days, this is the time period used to identify the timing of events in the cycle. However, the length of the menstrual cycle varies among women, and even in the same woman from one cycle to the next, typically from 21 to 32 days.

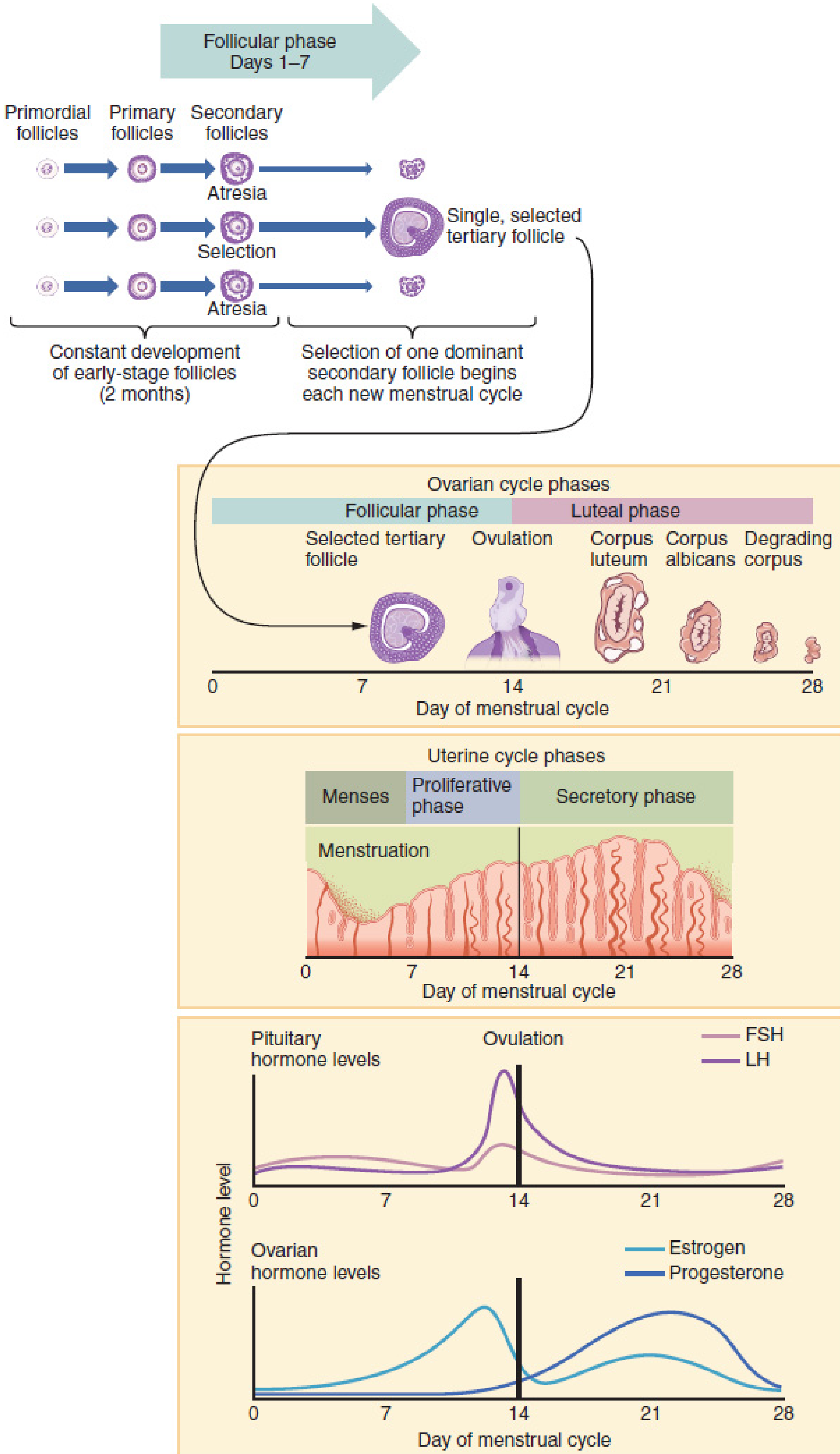
Just as the hormones produced by the granulosa and theca cells of the ovary “drive” the follicular and luteal phases of the ovarian cycle, they also control the three distinct phases of the menstrual cycle. These are the menses phase, the proliferative phase, and the secretory phase.

Menses Phase

The **menses phase** of the menstrual cycle is the phase during which the lining is shed; that is, the days that the woman menstruates. Although it averages approximately five days, the menses phase can last from 2 to 7 days, or longer. As shown in [link], the menses phase occurs during the

early days of the follicular phase of the ovarian cycle, when progesterone, FSH, and LH levels are low. Recall that progesterone concentrations decline as a result of the degradation of the corpus luteum, marking the end of the luteal phase. This decline in progesterone triggers the shedding of the stratum functionalis of the endometrium.

Hormone Levels in Ovarian and Menstrual Cycles


Follicular phase
Days 1–7
Primordial follicles
Primary follicles
Secondary follicles
Atresia
Single, selected tertiary follicle
Selection
Atresia
Constant development of early-stage follicles (2 months)
Selection of one dominant secondary follicle begins each new menstrual cycle
Ovarian cycle phases
Follicular phase
Luteal phase
Selected tertiary follicle
Ovulation
Corpus luteum
Corpus albicans
Degrading corpus
0
7
14
21
28
Day of menstrual cycle
Uterine cycle phases
Menses
Proliferative phase
Secretory phase
Menstruation
0
7
14
21
28
Day of menstrual cycle
Pituitary hormone levels
Ovulation
FSH
LH
0
7
14
21
28
Hormone level
Ovarian hormone levels
Estrogen
Progesterone
0
7
14
21
28
Day of menstrual cycle

The correlation of the hormone levels and their effects on the female reproductive system is shown in this timeline of the ovarian and menstrual cycles. The menstrual cycle begins at day one with the start of menses. Ovulation occurs around day 14 of a 28-day cycle, triggered by the LH surge.

Proliferative Phase

Once menstrual flow ceases, the endometrium begins to proliferate again, marking the beginning of the **proliferative phase** of the menstrual cycle (see [link]). It occurs when the granulosa and theca cells of the tertiary follicles begin to produce increased amounts of estrogen. These rising estrogen concentrations stimulate the endometrial lining to rebuild.

Recall that the high estrogen concentrations will eventually lead to a decrease in FSH as a result of negative feedback, resulting in atresia of all but one of the developing tertiary follicles. The switch to positive feedback—which occurs with the elevated estrogen production from the dominant follicle—then stimulates the LH surge that will trigger ovulation. In a typical 28-day menstrual cycle, ovulation occurs on day 14. Ovulation marks the end of the proliferative phase as well as the end of the follicular phase.

Secretory Phase

In addition to prompting the LH surge, high estrogen levels increase the uterine tube contractions that facilitate the pick-up and transfer of the ovulated oocyte. High estrogen levels also slightly decrease the acidity of the vagina, making it more hospitable to sperm. In the ovary, the luteinization of the granulosa cells of the collapsed follicle forms the

progesterone-producing corpus luteum, marking the beginning of the luteal phase of the ovarian cycle. In the uterus, progesterone from the corpus luteum begins the **secretory phase** of the menstrual cycle, in which the endometrial lining prepares for implantation (see [link]). Over the next 10 to 12 days, the endometrial glands secrete a fluid rich in glycogen. If fertilization has occurred, this fluid will nourish the ball of cells now developing from the zygote. At the same time, the spiral arteries develop to provide blood to the thickened stratum functionalis.

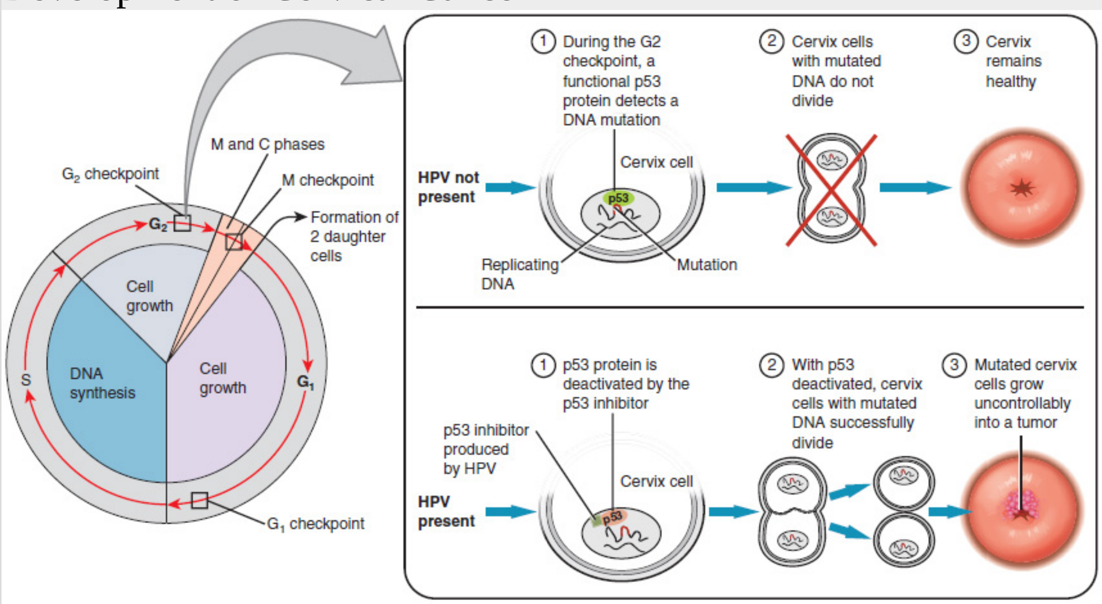
If no pregnancy occurs within approximately 10 to 12 days, the corpus luteum will degrade into the corpus albicans. Levels of both estrogen and progesterone will fall, and the endometrium will grow thinner. Prostaglandins will be secreted that cause constriction of the spiral arteries, reducing oxygen supply. The endometrial tissue will die, resulting in menses—or the first day of the next cycle.

Note:
Disorders of the… Feature
Female Reproductive System
Research over many years has confirmed that cervical cancer is most often caused by a sexually transmitted infection with human papillomavirus (HPV). There are over 100 related viruses in the HPV family, and the characteristics of each strain determine the outcome of the infection. In all cases, the virus enters body cells and uses its own genetic material to take over the host cell’s metabolic machinery and produce more virus particles.
HPV infections are common in both men and women. Indeed, a recent study determined that 42.5 percent of females had HPV at the time of testing. These women ranged in age from 14 to 59 years and differed in race, ethnicity, and number of sexual partners. Of note, the prevalence of HPV infection was 53.8 percent among women aged 20 to 24 years, the age group with the highest infection rate.
HPV strains are classified as high or low risk according to their potential to cause cancer. Though most HPV infections do not cause disease, the disruption of normal cellular functions in the low-risk forms of HPV can cause the male or female human host to develop genital warts. Often, the

body is able to clear an HPV infection by normal immune responses within 2 years. However, the more serious, high-risk infection by certain types of HPV can result in cancer of the cervix ([link]). Infection with either of the cancer-causing variants HPV 16 or HPV 18 has been linked to more than 70 percent of all cervical cancer diagnoses. Although even these high-risk HPV strains can be cleared from the body over time, infections persist in some individuals. If this happens, the HPV infection can influence the cells of the cervix to develop precancerous changes.

Risk factors for cervical cancer include having unprotected sex; having multiple sexual partners; a first sexual experience at a younger age, when the cells of the cervix are not fully mature; failure to receive the HPV vaccine; a compromised immune system; and smoking. The risk of developing cervical cancer is doubled with cigarette smoking.

Development of Cervical Cancer



In most cases, cells infected with the HPV virus heal on their own. In some cases, however, the virus continues to spread and becomes an invasive cancer.

When the high-risk types of HPV enter a cell, two viral proteins are used to neutralize proteins that the host cells use as checkpoints in the cell cycle. The best studied of these proteins is p53. In a normal cell, p53 detects DNA damage in the cell's genome and either halts the progression of the

cell cycle—allowing time for DNA repair to occur—or initiates apoptosis. Both of these processes prevent the accumulation of mutations in a cell’s genome. High-risk HPV can neutralize p53, keeping the cell in a state in which fast growth is possible and impairing apoptosis, allowing mutations to accumulate in the cellular DNA.

The prevalence of cervical cancer in the United States is very low because of regular screening exams called pap smears. Pap smears sample cells of the cervix, allowing the detection of abnormal cells. If pre-cancerous cells are detected, there are several highly effective techniques that are currently in use to remove them before they pose a danger. However, women in developing countries often do not have access to regular pap smears. As a result, these women account for as many as 80 percent of the cases of cervical cancer worldwide.

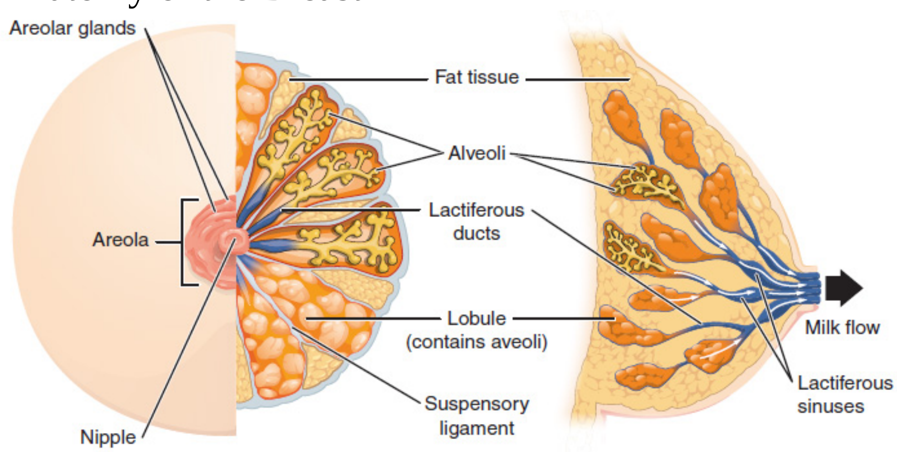
In 2006, the first vaccine against the high-risk types of HPV was approved. There are now two HPV vaccines available: Gardasil® and Cervarix®. Whereas these vaccines were initially only targeted for women, because HPV is sexually transmitted, both men and women require vaccination for this approach to achieve its maximum efficacy. A recent study suggests that the HPV vaccine has cut the rates of HPV infection by the four targeted strains at least in half. Unfortunately, the high cost of manufacturing the vaccine is currently limiting access to many women worldwide.

The Breasts

Whereas the breasts are located far from the other female reproductive organs, they are considered accessory organs of the female reproductive system. The function of the breasts is to supply milk to an infant in a process called lactation. The external features of the breast include a nipple surrounded by a pigmented **areola** ([link]), whose coloration may deepen during pregnancy. The areola is typically circular and can vary in size from 25 to 100 mm in diameter. The areolar region is characterized by small, raised areolar glands that secrete lubricating fluid during lactation to protect the nipple from chafing. When a baby nurses, or draws milk from the breast, the entire areolar region is taken into the mouth.

Breast milk is produced by the **mammary glands**, which are modified sweat glands. The milk itself exits the breast through the nipple via 15 to 20 **lactiferous ducts** that open on the surface of the nipple. These lactiferous ducts each extend to a **lactiferous sinus** that connects to a glandular lobe within the breast itself that contains groups of milk-secreting cells in clusters called **alveoli** (see [link]). The clusters can change in size depending on the amount of milk in the alveolar lumen. Once milk is made in the alveoli, stimulated myoepithelial cells that surround the alveoli contract to push the milk to the lactiferous sinuses. From here, the baby can draw milk through the lactiferous ducts by suckling. The lobes themselves are surrounded by fat tissue, which determines the size of the breast; breast size differs between individuals and does not affect the amount of milk produced. Supporting the breasts are multiple bands of connective tissue called **suspensory ligaments** that connect the breast tissue to the dermis of the overlying skin.

Anatomy of the Breast



During lactation, milk moves from the alveoli through the lactiferous ducts to the nipple.

During the normal hormonal fluctuations in the menstrual cycle, breast tissue responds to changing levels of estrogen and progesterone, which can lead to swelling and breast tenderness in some individuals, especially during the secretory phase. If pregnancy occurs, the increase in hormones

leads to further development of the mammary tissue and enlargement of the breasts.

Hormonal Birth Control

Birth control pills take advantage of the negative feedback system that regulates the ovarian and menstrual cycles to stop ovulation and prevent pregnancy. Typically they work by providing a constant level of both estrogen and progesterone, which negatively feeds back onto the hypothalamus and pituitary, thus preventing the release of FSH and LH. Without FSH, the follicles do not mature, and without the LH surge, ovulation does not occur. Although the estrogen in birth control pills does stimulate some thickening of the endometrial wall, it is reduced compared with a normal cycle and is less likely to support implantation.

Some birth control pills contain 21 active pills containing hormones, and 7 inactive pills (placebos). The decline in hormones during the week that the woman takes the placebo pills triggers menses, although it is typically lighter than a normal menstrual flow because of the reduced endometrial thickening. Newer types of birth control pills have been developed that deliver low-dose estrogens and progesterone for the entire cycle (these are meant to be taken 365 days a year), and menses never occurs. While some women prefer to have the proof of a lack of pregnancy that a monthly period provides, menstruation every 28 days is not required for health reasons, and there are no reported adverse effects of not having a menstrual period in an otherwise healthy individual.

Because birth control pills function by providing constant estrogen and progesterone levels and disrupting negative feedback, skipping even just one or two pills at certain points of the cycle (or even being several hours late taking the pill) can lead to an increase in FSH and LH and result in ovulation. It is important, therefore, that the woman follow the directions on the birth control pill package to successfully prevent pregnancy.

Note:

Aging and the… Feature

Female Reproductive System

Female fertility (the ability to conceive) peaks when women are in their twenties, and is slowly reduced until a women reaches 35 years of age. After that time, fertility declines more rapidly, until it ends completely at the end of menopause. Menopause is the cessation of the menstrual cycle that occurs as a result of the loss of ovarian follicles and the hormones that they produce. A woman is considered to have completed menopause if she has not menstruated in a full year. After that point, she is considered postmenopausal. The average age for this change is consistent worldwide at between 50 and 52 years of age, but it can normally occur in a woman’s forties, or later in her fifties. Poor health, including smoking, can lead to earlier loss of fertility and earlier menopause.

As a woman reaches the age of menopause, depletion of the number of viable follicles in the ovaries due to atresia affects the hormonal regulation of the menstrual cycle. During the years leading up to menopause, there is a decrease in the levels of the hormone inhibin, which normally participates in a negative feedback loop to the pituitary to control the production of FSH. The menopausal decrease in inhibin leads to an increase in FSH. The presence of FSH stimulates more follicles to grow and secrete estrogen. Because small, secondary follicles also respond to increases in FSH levels, larger numbers of follicles are stimulated to grow; however, most undergo atresia and die. Eventually, this process leads to the depletion of all follicles in the ovaries, and the production of estrogen falls off dramatically. It is primarily the lack of estrogens that leads to the symptoms of menopause.

The earliest changes occur during the menopausal transition, often referred to as peri-menopause, when a women’s cycle becomes irregular but does not stop entirely. Although the levels of estrogen are still nearly the same as before the transition, the level of progesterone produced by the corpus luteum is reduced. This decline in progesterone can lead to abnormal growth, or hyperplasia, of the endometrium. This condition is a concern because it increases the risk of developing endometrial cancer. Two harmless conditions that can develop during the transition are uterine fibroids, which are benign masses of cells, and irregular bleeding. As estrogen levels change, other symptoms that occur are hot flashes and night sweats, trouble sleeping, vaginal dryness, mood swings, difficulty

focusing, and thinning of hair on the head along with the growth of more hair on the face. Depending on the individual, these symptoms can be entirely absent, moderate, or severe.

After menopause, lower amounts of estrogens can lead to other changes. Cardiovascular disease becomes as prevalent in women as in men, possibly because estrogens reduce the amount of cholesterol in the blood vessels. When estrogen is lacking, many women find that they suddenly have problems with high cholesterol and the cardiovascular issues that accompany it. Osteoporosis is another problem because bone density decreases rapidly in the first years after menopause. The reduction in bone density leads to a higher incidence of fractures.

Hormone therapy (HT), which employs medication (synthetic estrogens and progestins) to increase estrogen and progestin levels, can alleviate some of the symptoms of menopause. In 2002, the Women’s Health Initiative began a study to observe women for the long-term outcomes of hormone replacement therapy over 8.5 years. However, the study was prematurely terminated after 5.2 years because of evidence of a higher than normal risk of breast cancer in patients taking estrogen-only HT. The potential positive effects on cardiovascular disease were also not realized in the estrogen-only patients. The results of other hormone replacement studies over the last 50 years, including a 2012 study that followed over 1,000 menopausal women for 10 years, have shown cardiovascular benefits from estrogen and no increased risk for cancer. Some researchers believe that the age group tested in the 2002 trial may have been too old to benefit from the therapy, thus skewing the results. In the meantime, intense debate and study of the benefits and risks of replacement therapy is ongoing. Current guidelines approve HT for the reduction of hot flashes or flushes, but this treatment is generally only considered when women first start showing signs of menopausal changes, is used in the lowest dose possible for the shortest time possible (5 years or less), and it is suggested that women on HT have regular pelvic and breast exams.

Chapter Review

The external female genitalia are collectively called the vulva. The vagina is the pathway into and out of the uterus. The man’s penis is inserted into the vagina to deliver sperm, and the baby exits the uterus through the vagina during childbirth.

The ovaries produce oocytes, the female gametes, in a process called oogenesis. As with spermatogenesis, meiosis produces the haploid gamete (in this case, an ovum); however, it is completed only in an oocyte that has been penetrated by a sperm. In the ovary, an oocyte surrounded by supporting cells is called a follicle. In folliculogenesis, primordial follicles develop into primary, secondary, and tertiary follicles. Early tertiary follicles with their fluid-filled antrum will be stimulated by an increase in FSH, a gonadotropin produced by the anterior pituitary, to grow in the 28-day ovarian cycle. Supporting granulosa and theca cells in the growing follicles produce estrogens, until the level of estrogen in the bloodstream is high enough that it triggers negative feedback at the hypothalamus and pituitary. This results in a reduction of FSH and LH, and most tertiary follicles in the ovary undergo atresia (they die). One follicle, usually the one with the most FSH receptors, survives this period and is now called the dominant follicle. The dominant follicle produces more estrogen, triggering positive feedback and the LH surge that will induce ovulation. Following ovulation, the granulosa cells of the empty follicle luteinize and transform into the progesterone-producing corpus luteum. The ovulated oocyte with its surrounding granulosa cells is picked up by the infundibulum of the uterine tube, and beating cilia help to transport it through the tube toward the uterus. Fertilization occurs within the uterine tube, and the final stage of meiosis is completed.

The uterus has three regions: the fundus, the body, and the cervix. It has three layers: the outer perimetrium, the muscular myometrium, and the inner endometrium. The endometrium responds to estrogen released by the follicles during the menstrual cycle and grows thicker with an increase in blood vessels in preparation for pregnancy. If the egg is not fertilized, no signal is sent to extend the life of the corpus luteum, and it degrades, stopping progesterone production. This decline in progesterone results in the sloughing of the inner portion of the endometrium in a process called menses, or menstruation.

The breasts are accessory sexual organs that are utilized after the birth of a child to produce milk in a process called lactation. Birth control pills provide constant levels of estrogen and progesterone to negatively feed back on the hypothalamus and pituitary, and suppress the release of FSH and LH, which inhibits ovulation and prevents pregnancy.

Interactive Link Questions

Exercise:

Problem:

Watch this video to observe ovulation and its initiation in response to the release of FSH and LH from the pituitary gland. What specialized structures help guide the oocyte from the ovary into the uterine tube?

Solution:

The fimbriae sweep the oocyte into the uterine tube.

Exercise:

Problem:

Watch this series of videos to look at the movement of the oocyte through the ovary. The cilia in the uterine tube promote movement of the oocyte. What would likely occur if the cilia were paralyzed at the time of ovulation?

Solution:

The oocyte may not enter the tube and may enter the pelvic cavity.

Review Questions

Exercise:

Problem: What are the female gonads called?

a. oocytes
b. ova
c. oviducts
d. ovaries

Solution:

d

Exercise:

Problem: When do the oogonia undergo mitosis?

a. before birth
b. at puberty
c. at the beginning of each menstrual cycle
d. during fertilization

Solution:

a

Exercise:

Problem: From what structure does the corpus luteum originate?

a. uterine corpus
b. dominant follicle
c. fallopian tube
d. corpus albicans

Solution:

b

Exercise:

Problem:

Where does fertilization of the egg by the sperm typically occur?

a. vagina
b. uterus
c. uterine tube
d. ovary

Solution:

c

Exercise:

Problem: Why do estrogen levels fall after menopause?

a. The ovaries degrade.
b. There are no follicles left to produce estrogen.
c. The pituitary secretes a menopause-specific hormone.
d. The cells of the endometrium degenerate.

Solution:

b

Exercise:

Problem: The vulva includes the _________.

a. lactiferous duct, rugae, and hymen
b. lactiferous duct, endometrium, and bulbourethral glands
c. mons pubis, endometrium, and hymen
d. mons pubis, labia majora, and Bartholin’s glands

Solution:

d

Critical Thinking Questions

Exercise:

Problem:

Follow the path of ejaculated sperm from the vagina to the oocyte. Include all structures of the female reproductive tract that the sperm must swim through to reach the egg.

Solution:

The sperm must swim upward in the vagina, through the cervix, and then through the body of the uterus to one or the other of the two uterine tubes. Fertilization generally occurs in the uterine tube.

Exercise:

Problem:

Identify some differences between meiosis in men and women.

Solution:

Meiosis in the man results in four viable haploid sperm, whereas meiosis in the woman results in a secondary oocyte and, upon completion following fertilization by a sperm, one viable haploid ovum with abundant cytoplasm and up to three polar bodies with little cytoplasm that are destined to die.

Exercise:

Problem:

Explain the hormonal regulation of the phases of the menstrual cycle.

Solution:

As a result of the degradation of the corpus luteum, a decline in progesterone concentrations triggers the shedding of the endometrial lining, marking the menses phase of the menstrual cycle. Low progesterone levels also reduce the negative feedback that had been occurring at the hypothalamus and pituitary, and result in the release of GnRH and, subsequently, FSH and LH. FSH stimulates tertiary follicles to grow and granulosa and theca cells begin to produce increased amounts of estrogen. High estrogen concentrations stimulate the endometrial lining to rebuild, marking the proliferative phase of the menstrual cycle. The high estrogen concentrations will eventually lead to a decrease in FSH because of negative feedback, resulting in atresia of all but one of the developing tertiary follicles. The switch to positive feedback that occurs with elevated estrogen production from the dominant follicle stimulates the LH surge that will trigger ovulation. The luteinization of the granulosa cells of the collapsed follicle forms the progesterone-producing corpus luteum. Progesterone from the corpus luteum causes the endometrium to prepare for implantation, in part by secreting nutrient-rich fluid. This marks the secretory phase of the menstrual cycle. Finally, in a non-fertile cycle, the corpus luteum will degrade and menses will occur.

Exercise:

Problem:

Endometriosis is a disorder in which endometrial cells implant and proliferate outside of the uterus—in the uterine tubes, on the ovaries, or even in the pelvic cavity. Offer a theory as to why endometriosis increases a woman’s risk of infertility.

Solution:

Endometrial tissue proliferating outside of the endometrium—for example, in the uterine tubes, on the ovaries, or within the pelvic cavity—could block the passage of sperm, ovulated oocytes, or a zygote, thus reducing fertility.

Glossary

alveoli
: (of the breast) milk-secreting cells in the mammary gland

ampulla
: (of the uterine tube) middle portion of the uterine tube in which fertilization often occurs

antrum
: fluid-filled chamber that characterizes a mature tertiary (antral) follicle

areola
: highly pigmented, circular area surrounding the raised nipple and containing areolar glands that secrete fluid important for lubrication during suckling

Bartholin’s glands
: (also, greater vestibular glands) glands that produce a thick mucus that maintains moisture in the vulva area; also referred to as the greater vestibular glands

body of uterus
: middle section of the uterus

broad ligament
: wide ligament that supports the uterus by attaching laterally to both sides of the uterus and pelvic wall

cervix
: elongate inferior end of the uterus where it connects to the vagina

clitoris
: (also, glans clitoris) nerve-rich area of the vulva that contributes to sexual sensation during intercourse

corpus albicans

nonfunctional structure remaining in the ovarian stroma following structural and functional regression of the corpus luteum

corpus luteum
: transformed follicle after ovulation that secretes progesterone

endometrium
: inner lining of the uterus, part of which builds up during the secretory phase of the menstrual cycle and then sheds with menses

fimbriae
: fingerlike projections on the distal uterine tubes

follicle
: ovarian structure of one oocyte and surrounding granulosa (and later theca) cells

folliculogenesis
: development of ovarian follicles from primordial to tertiary under the stimulation of gonadotropins

fundus
: (of the uterus) domed portion of the uterus that is superior to the uterine tubes

granulosa cells
: supportive cells in the ovarian follicle that produce estrogen

hymen
: membrane that covers part of the opening of the vagina

infundibulum
: (of the uterine tube) wide, distal portion of the uterine tube terminating in fimbriae

isthmus
: narrow, medial portion of the uterine tube that joins the uterus

labia majora

hair-covered folds of skin located behind the mons pubis

labia minora
thin, pigmented, hairless flaps of skin located medial and deep to the labia majora

lactiferous ducts
ducts that connect the mammary glands to the nipple and allow for the transport of milk

lactiferous sinus
area of milk collection between alveoli and lactiferous duct

mammary glands
glands inside the breast that secrete milk

menarche
first menstruation in a pubertal female

menses
shedding of the inner portion of the endometrium out though the vagina; also referred to as menstruation

menses phase
phase of the menstrual cycle in which the endometrial lining is shed

menstrual cycle
approximately 28-day cycle of changes in the uterus consisting of a menses phase, a proliferative phase, and a secretory phase

mons pubis
mound of fatty tissue located at the front of the vulva

myometrium
smooth muscle layer of uterus that allows for uterine contractions during labor and expulsion of menstrual blood

oocyte

cell that results from the division of the oogonium and undergoes meiosis I at the LH surge and meiosis II at fertilization to become a haploid ovum

oogenesis
: process by which oogonia divide by mitosis to primary oocytes, which undergo meiosis to produce the secondary oocyte and, upon fertilization, the ovum

oogonia
: ovarian stem cells that undergo mitosis during female fetal development to form primary oocytes

ovarian cycle
: approximately 28-day cycle of changes in the ovary consisting of a follicular phase and a luteal phase

ovaries
: female gonads that produce oocytes and sex steroid hormones (notably estrogen and progesterone)

ovulation
: release of a secondary oocyte and associated granulosa cells from an ovary

ovum
: haploid female gamete resulting from completion of meiosis II at fertilization

perimetrium
: outer epithelial layer of uterine wall

polar body
: smaller cell produced during the process of meiosis in oogenesis

primary follicles
: ovarian follicles with a primary oocyte and one layer of cuboidal granulosa cells

primordial follicles
: least developed ovarian follicles that consist of a single oocyte and a single layer of flat (squamous) granulosa cells

proliferative phase
: phase of the menstrual cycle in which the endometrium proliferates

rugae
: (of the vagina) folds of skin in the vagina that allow it to stretch during intercourse and childbirth

secondary follicles
: ovarian follicles with a primary oocyte and multiple layers of granulosa cells

secretory phase
: phase of the menstrual cycle in which the endometrium secretes a nutrient-rich fluid in preparation for implantation of an embryo

suspensory ligaments
: bands of connective tissue that suspend the breast onto the chest wall by attachment to the overlying dermis

tertiary follicles
: (also, antral follicles) ovarian follicles with a primary or secondary oocyte, multiple layers of granulosa cells, and a fully formed antrum

theca cells
: estrogen-producing cells in a maturing ovarian follicle

uterine tubes
: (also, fallopian tubes or oviducts) ducts that facilitate transport of an ovulated oocyte to the uterus

uterus
: muscular hollow organ in which a fertilized egg develops into a fetus

vagina

tunnel-like organ that provides access to the uterus for the insertion of semen and from the uterus for the birth of a baby

vulva
: external female genitalia

Development of the Male and Female Reproductive Systems
By the end of this section, you will be able to:

- Explain how bipotential tissues are directed to develop into male or female sex organs
- Name the rudimentary duct systems in the embryo that are precursors to male or female internal sex organs
- Describe the hormonal changes that bring about puberty, and the secondary sex characteristics of men and women

The development of the reproductive systems begins soon after fertilization of the egg, with primordial gonads beginning to develop approximately one month after conception. Reproductive development continues in utero, but there is little change in the reproductive system between infancy and puberty.

Development of the Sexual Organs in the Embryo and Fetus

Females are considered the "fundamental" sex—that is, without much chemical prompting, all fertilized eggs would develop into females. To become a male, an individual must be exposed to the cascade of factors initiated by a single gene on the male Y chromosome. This is called the SRY (*S*ex-determining *R*egion of the *Y* chromosome). Because females do not have a Y chromosome, they do not have the *SRY* gene. Without a functional *SRY* gene, an individual will be female.

In both male and female embryos, the same group of cells has the potential to develop into either the male or female gonads; this tissue is considered bipotential. The *SRY* gene actively recruits other genes that begin to develop the testes, and suppresses genes that are important in female development. As part of this *SRY*-prompted cascade, germ cells in the bipotential gonads differentiate into spermatogonia. Without *SRY*, different genes are expressed, oogonia form, and primordial follicles develop in the primitive ovary.

Soon after the formation of the testis, the Leydig cells begin to secrete testosterone. Testosterone can influence tissues that are bipotential to

become male reproductive structures. For example, with exposure to testosterone, cells that could become either the glans penis or the glans clitoris form the glans penis. Without testosterone, these same cells differentiate into the clitoris.

Not all tissues in the reproductive tract are bipotential. The internal reproductive structures (for example the uterus, uterine tubes, and part of the vagina in females; and the epididymis, ductus deferens, and seminal vesicles in males) form from one of two rudimentary duct systems in the embryo. For proper reproductive function in the adult, one set of these ducts must develop properly, and the other must degrade. In males, secretions from sustentacular cells trigger a degradation of the female duct, called the **Müllerian duct**. At the same time, testosterone secretion stimulates growth of the male tract, the **Wolffian duct**. Without such sustentacular cell secretion, the Müllerian duct will develop; without testosterone, the Wolffian duct will degrade. Thus, the developing offspring will be female. For more information and a figure of differentiation of the gonads, seek additional content on fetal development.

Note:
Interactive Link Feature

A baby’s gender is determined at conception, and the different genitalia of male and female fetuses develop from the same tissues in the embryo. View this animation to see a comparison of the development of structures of the female and male reproductive systems in a growing fetus. Where are the testes located for most of gestational time?

Further Sexual Development Occurs at Puberty

Puberty is the stage of development at which individuals become sexually mature. Though the outcomes of puberty for boys and girls are very different, the hormonal control of the process is very similar. In addition, though the timing of these events varies between individuals, the sequence of changes that occur is predictable for male and female adolescents. As shown in [link], a concerted release of hormones from the hypothalamus (GnRH), the anterior pituitary (LH and FSH), and the gonads (either testosterone or estrogen) is responsible for the maturation of the reproductive systems and the development of **secondary sex characteristics**, which are physical changes that serve auxiliary roles in reproduction.

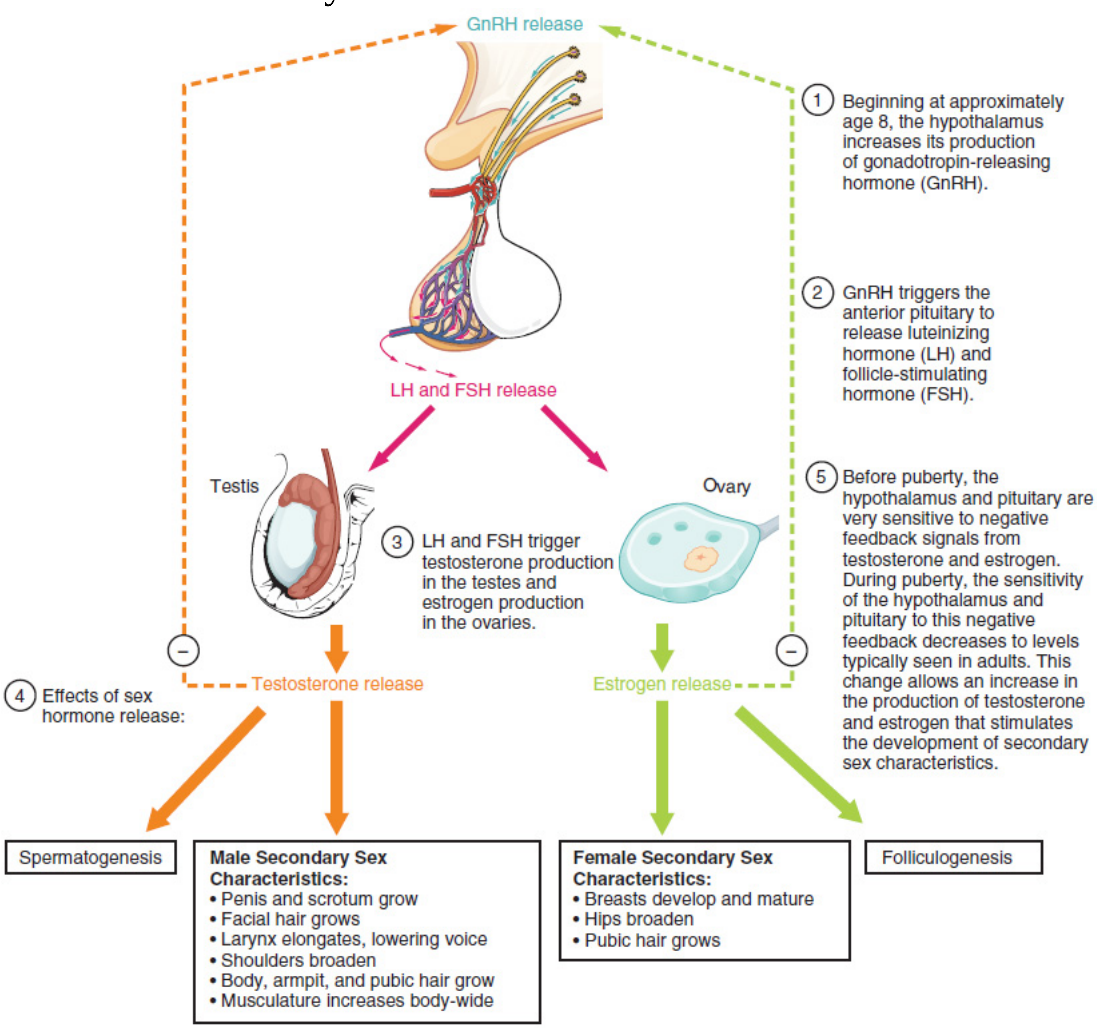
The first changes begin around the age of eight or nine when the production of LH becomes detectable. The release of LH occurs primarily at night during sleep and precedes the physical changes of puberty by several years. In pre-pubertal children, the sensitivity of the negative feedback system in the hypothalamus and pituitary is very high. This means that very low concentrations of androgens or estrogens will negatively feed back onto the hypothalamus and pituitary, keeping the production of GnRH, LH, and FSH low.

As an individual approaches puberty, two changes in sensitivity occur. The first is a decrease of sensitivity in the hypothalamus and pituitary to negative feedback, meaning that it takes increasingly larger concentrations of sex steroid hormones to stop the production of LH and FSH. The second change in sensitivity is an increase in sensitivity of the gonads to the FSH and LH signals, meaning the gonads of adults are more responsive to gonadotropins than are the gonads of children. As a result of these two changes, the levels of LH and FSH slowly increase and lead to the enlargement and maturation of the gonads, which in turn leads to secretion of higher levels of sex hormones and the initiation of spermatogenesis and folliculogenesis.

In addition to age, multiple factors can affect the age of onset of puberty, including genetics, environment, and psychological stress. One of the more

important influences may be nutrition; historical data demonstrate the effect of better and more consistent nutrition on the age of menarche in girls in the United States, which decreased from an average age of approximately 17 years of age in 1860 to the current age of approximately 12.75 years in 1960, as it remains today. Some studies indicate a link between puberty onset and the amount of stored fat in an individual. This effect is more pronounced in girls, but has been documented in both sexes. Body fat, corresponding with secretion of the hormone leptin by adipose cells, appears to have a strong role in determining menarche. This may reflect to some extent the high metabolic costs of gestation and lactation. In girls who are lean and highly active, such as gymnasts, there is often a delay in the onset of puberty.

Hormones of Puberty



During puberty, the release of LH and FSH from the anterior

pituitary stimulates the gonads to produce sex hormones in both male and female adolescents.

Signs of Puberty

Different sex steroid hormone concentrations between the sexes also contribute to the development and function of secondary sexual characteristics. Examples of secondary sexual characteristics are listed in [link].

Development of the Secondary Sexual Characteristics	
Male	**Female**
Increased larynx size and deepening of the voice	Deposition of fat, predominantly in breasts and hips
Increased muscular development	Breast development
Growth of facial, axillary, and pubic hair, and increased growth of body hair	Broadening of the pelvis and growth of axillary and pubic hair

As a girl reaches puberty, typically the first change that is visible is the development of the breast tissue. This is followed by the growth of axillary and pubic hair. A growth spurt normally starts at approximately age 9 to 11, and may last two years or more. During this time, a girl's height can

increase 3 inches a year. The next step in puberty is menarche, the start of menstruation.

In boys, the growth of the testes is typically the first physical sign of the beginning of puberty, which is followed by growth and pigmentation of the scrotum and growth of the penis. The next step is the growth of hair, including armpit, pubic, chest, and facial hair. Testosterone stimulates the growth of the larynx and thickening and lengthening of the vocal folds, which causes the voice to drop in pitch. The first fertile ejaculations typically appear at approximately 15 years of age, but this age can vary widely across individual boys. Unlike the early growth spurt observed in females, the male growth spurt occurs toward the end of puberty, at approximately age 11 to 13, and a boy’s height can increase as much as 4 inches a year. In some males, pubertal development can continue through the early 20s.

Chapter Review

The reproductive systems of males and females begin to develop soon after conception. A gene on the male’s Y chromosome called *SRY* is critical in stimulating a cascade of events that simultaneously stimulate testis development and repress the development of female structures. Testosterone produced by Leydig cells in the embryonic testis stimulates the development of male sexual organs. If testosterone is not present, female sexual organs will develop.

Whereas the gonads and some other reproductive tissues are considered bipotential, the tissue that forms the internal reproductive structures stems from ducts that will develop into only male (Wolffian) or female (Müllerian) structures. To be able to reproduce as an adult, one of these systems must develop properly and the other must degrade.

Further development of the reproductive systems occurs at puberty. The initiation of the changes that occur in puberty is the result of a decrease in sensitivity to negative feedback in the hypothalamus and pituitary gland, and an increase in sensitivity of the gonads to FSH and LH stimulation. These changes lead to increases in either estrogen or testosterone, in female

and male adolescents, respectively. The increase in sex steroid hormones leads to maturation of the gonads and other reproductive organs. The initiation of spermatogenesis begins in boys, and girls begin ovulating and menstruating. Increases in sex steroid hormones also lead to the development of secondary sex characteristics such as breast development in girls and facial hair and larynx growth in boys.

Interactive Link Questions

Exercise:

Problem:

A baby's gender is determined at conception, and the different genitalia of male and female fetuses develop from the same tissues in the embryo. View this animation that compares the development of structures of the female and male reproductive systems in a growing fetus. Where are the testes located for most of gestational time?

Solution:

The testes are located in the abdomen.

Review Questions

Exercise:

Problem:

What controls whether an embryo will develop testes or ovaries?

a. pituitary gland
b. hypothalamus
c. Y chromosome
d. presence or absence of estrogen

Solution:

c

Exercise:

Problem: Without *SRY* expression, an embryo will develop ________.

a. male reproductive structures
b. female reproductive structures
c. no reproductive structures
d. male reproductive structures 50 percent of the time and female reproductive structures 50 percent of the time

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Solution:

b

Exercise:

Problem:

The timing of puberty can be influenced by which of the following?

a. genes
b. stress
c. amount of body fat
d. all of the above

Solution:

d

Critical Thinking Questions

Exercise:

Problem:

Identify the changes in sensitivity that occur in the hypothalamus, pituitary, and gonads as a boy or girl approaches puberty. Explain how these changes lead to the increases of sex steroid hormone secretions that drive many pubertal changes.

Solution:

As an individual approaches puberty, two changes in sensitivity occur. The first is a decrease of sensitivity in the hypothalamus and pituitary to negative feedback, meaning that it takes increasingly larger concentrations of sex steroid hormones to stop the production of LH and FSH. The second change in sensitivity is an increase in the sensitivity of the gonads to the FSH and LH signals, meaning that the gonads of adults are more responsive to gonadotropins than are the gonads of children. As a result of these two changes, the levels of LH and FSH slowly increase and lead to the enlargement and maturation of the gonads, which in turn leads to secretion of higher levels of sex hormones and the initiation of spermatogenesis and folliculogenesis.

Exercise:

Problem:

Explain how the internal female and male reproductive structures develop from two different duct systems.

Solution:

The internal reproductive structures form from one of two rudimentary duct systems in the embryo. Testosterone secretion stimulates growth of the male tract, the Wolffian duct. Secretions of sustentacular cells trigger a degradation of the female tract, the Müllerian duct. Without these stimuli, the Müllerian duct will develop and the Wolffian duct will degrade, resulting in a female embryo.

Exercise:

Problem:

Explain what would occur during fetal development to an XY individual with a mutation causing a nonfunctional *SRY* gene.

Solution:

If the *SRY* gene were not functional, the XY individual would be genetically a male, but would develop female reproductive structures.

Glossary

Müllerian duct
: duct system present in the embryo that will eventually form the internal female reproductive structures

puberty
: life stage during which a male or female adolescent becomes anatomically and physiologically capable of reproduction

secondary sex characteristics
: physical characteristics that are influenced by sex steroid hormones and have supporting roles in reproductive function

Wolffian duct
: duct system present in the embryo that will eventually form the internal male reproductive structures

Fertilization
By the end of this section, you will be able to:

- Describe the obstacles that sperm must overcome to reach an oocyte
- Explain capacitation and its importance in fertilization
- Summarize the events that occur as a sperm fertilizes an oocyte

Fertilization occurs when a sperm and an oocyte (egg) combine and their nuclei fuse. Because each of these reproductive cells is a haploid cell containing half of the genetic material needed to form a human being, their combination forms a diploid cell. This new single cell, called a **zygote**, contains all of the genetic material needed to form a human—half from the mother and half from the father.

Transit of Sperm

Fertilization is a numbers game. During ejaculation, hundreds of millions of sperm (spermatozoa) are released into the vagina. Almost immediately, millions of these sperm are overcome by the acidity of the vagina (approximately pH 3.8), and millions more may be blocked from entering the uterus by thick cervical mucus. Of those that do enter, thousands are destroyed by phagocytic uterine leukocytes. Thus, the race into the uterine tubes, which is the most typical site for sperm to encounter the oocyte, is reduced to a few thousand contenders. Their journey—thought to be facilitated by uterine contractions—usually takes from 30 minutes to 2 hours. If the sperm do not encounter an oocyte immediately, they can survive in the uterine tubes for another 3–5 days. Thus, fertilization can still occur if intercourse takes place a few days before ovulation. In comparison, an oocyte can survive independently for only approximately 24 hours following ovulation. Intercourse more than a day after ovulation will therefore usually not result in fertilization.

During the journey, fluids in the female reproductive tract prepare the sperm for fertilization through a process called **capacitation**, or priming. The fluids improve the motility of the spermatozoa. They also deplete cholesterol molecules embedded in the membrane of the head of the sperm, thinning the membrane in such a way that will help facilitate the release of

the lysosomal (digestive) enzymes needed for the sperm to penetrate the oocyte’s exterior once contact is made. Sperm must undergo the process of capacitation in order to have the “capacity” to fertilize an oocyte. If they reach the oocyte before capacitation is complete, they will be unable to penetrate the oocyte’s thick outer layer of cells.

Contact Between Sperm and Oocyte

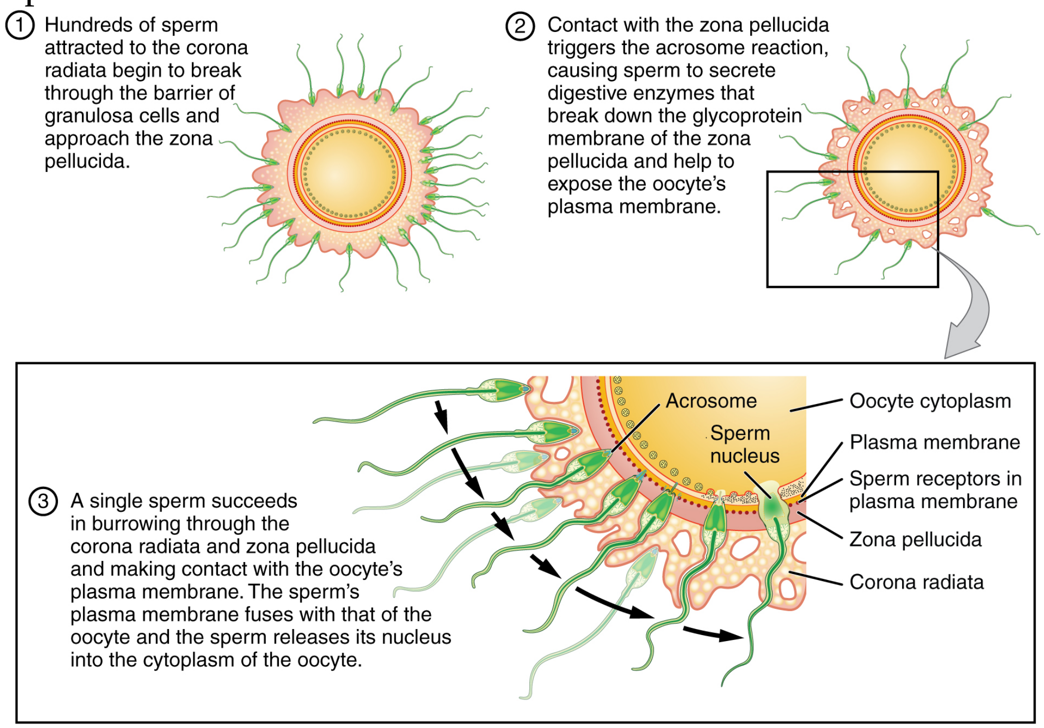
Upon ovulation, the oocyte released by the ovary is swept into—and along—the uterine tube. Fertilization must occur in the distal uterine tube because an unfertilized oocyte cannot survive the 72-hour journey to the uterus. As you will recall from your study of the oogenesis, this oocyte (specifically a secondary oocyte) is surrounded by two protective layers. The **corona radiata** is an outer layer of follicular (granulosa) cells that form around a developing oocyte in the ovary and remain with it upon ovulation. The underlying **zona pellucida** (pellucid = “transparent”) is a transparent, but thick, glycoprotein membrane that surrounds the cell’s plasma membrane.

As it is swept along the distal uterine tube, the oocyte encounters the surviving capacitated sperm, which stream toward it in response to chemical attractants released by the cells of the corona radiata. To reach the oocyte itself, the sperm must penetrate the two protective layers. The sperm first burrow through the cells of the corona radiata. Then, upon contact with the zona pellucida, the sperm bind to receptors in the zona pellucida. This initiates a process called the **acrosomal reaction** in which the enzyme-filled “cap” of the sperm, called the **acrosome**, releases its stored digestive enzymes. These enzymes clear a path through the zona pellucida that allows sperm to reach the oocyte. Finally, a single sperm makes contact with sperm-binding receptors on the oocyte’s plasma membrane ([link]). The plasma membrane of that sperm then fuses with the oocyte’s plasma membrane, and the head and mid-piece of the “winning” sperm enter the oocyte interior.

How do sperm penetrate the corona radiata? Some sperm undergo a spontaneous acrosomal reaction, which is an acrosomal reaction not triggered by contact with the zona pellucida. The digestive enzymes

released by this reaction digest the extracellular matrix of the corona radiata. As you can see, the first sperm to reach the oocyte is never the one to fertilize it. Rather, hundreds of sperm cells must undergo the acrosomal reaction, each helping to degrade the corona radiata and zona pellucida until a path is created to allow one sperm to contact and fuse with the plasma membrane of the oocyte. If you consider the loss of millions of sperm between entry into the vagina and degradation of the zona pellucida, you can understand why a low sperm count can cause male infertility.

Sperm and the Process of Fertilization



Before fertilization, hundreds of capacitated sperm must break through the surrounding corona radiata and zona pellucida so that one can contact and fuse with the oocyte plasma membrane.

When the first sperm fuses with the oocyte, the oocyte deploys two mechanisms to prevent **polyspermy**, which is penetration by more than one sperm. This is critical because if more than one sperm were to fertilize the

oocyte, the resulting zygote would be a triploid organism with three sets of chromosomes. This is incompatible with life.

The first mechanism is the fast block, which involves a near instantaneous change in sodium ion permeability upon binding of the first sperm, depolarizing the oocyte plasma membrane and preventing the fusion of additional sperm cells. The fast block sets in almost immediately and lasts for about a minute, during which time an influx of calcium ions following sperm penetration triggers the second mechanism, the slow block. In this process, referred to as the **cortical reaction**, cortical granules sitting immediately below the oocyte plasma membrane fuse with the membrane and release zonal inhibiting proteins and mucopolysaccharides into the space between the plasma membrane and the zona pellucida. Zonal inhibiting proteins cause the release of any other attached sperm and destroy the oocyte’s sperm receptors, thus preventing any more sperm from binding. The mucopolysaccharides then coat the nascent zygote in an impenetrable barrier that, together with hardened zona pellucida, is called a **fertilization membrane**.

The Zygote

Recall that at the point of fertilization, the oocyte has not yet completed meiosis; all secondary oocytes remain arrested in metaphase of meiosis II until fertilization. Only upon fertilization does the oocyte complete meiosis. The unneeded complement of genetic material that results is stored in a second polar body that is eventually ejected. At this moment, the oocyte has become an ovum, the female haploid gamete. The two haploid nuclei derived from the sperm and oocyte and contained within the egg are referred to as pronuclei. They decondense, expand, and replicate their DNA in preparation for mitosis. The pronuclei then migrate toward each other, their nuclear envelopes disintegrate, and the male- and female-derived genetic material intermingles. This step completes the process of fertilization and results in a single-celled diploid zygote with all the genetic instructions it needs to develop into a human.

Most of the time, a woman releases a single egg during an ovulation cycle. However, in approximately 1 percent of ovulation cycles, two eggs are

released and both are fertilized. Two zygotes form, implant, and develop, resulting in the birth of dizygotic (or fraternal) twins. Because dizygotic twins develop from two eggs fertilized by two sperm, they are no more identical than siblings born at different times.

Much less commonly, a zygote can divide into two separate offspring during early development. This results in the birth of monozygotic (or identical) twins. Although the zygote can split as early as the two-cell stage, splitting occurs most commonly during the early blastocyst stage, with roughly 70–100 cells present. These two scenarios are distinct from each other, in that the twin embryos that separated at the two-cell stage will have individual placentas, whereas twin embryos that form from separation at the blastocyst stage will share a placenta and a chorionic cavity.

Note:
Everyday Connections
In Vitro Fertilization
IVF, which stands for in vitro fertilization, is an assisted reproductive technology. In vitro, which in Latin translates to “in glass,” refers to a procedure that takes place outside of the body. There are many different indications for IVF. For example, a woman may produce normal eggs, but the eggs cannot reach the uterus because the uterine tubes are blocked or otherwise compromised. A man may have a low sperm count, low sperm motility, sperm with an unusually high percentage of morphological abnormalities, or sperm that are incapable of penetrating the zona pellucida of an egg.

A typical IVF procedure begins with egg collection. A normal ovulation cycle produces only one oocyte, but the number can be boosted significantly (to 10–20 oocytes) by administering a short course of gonadotropins. The course begins with follicle-stimulating hormone (FSH) analogs, which support the development of multiple follicles, and ends with a luteinizing hormone (LH) analog that triggers ovulation. Right before the ova would be released from the ovary, they are harvested using ultrasound-guided oocyte retrieval. In this procedure, ultrasound allows a

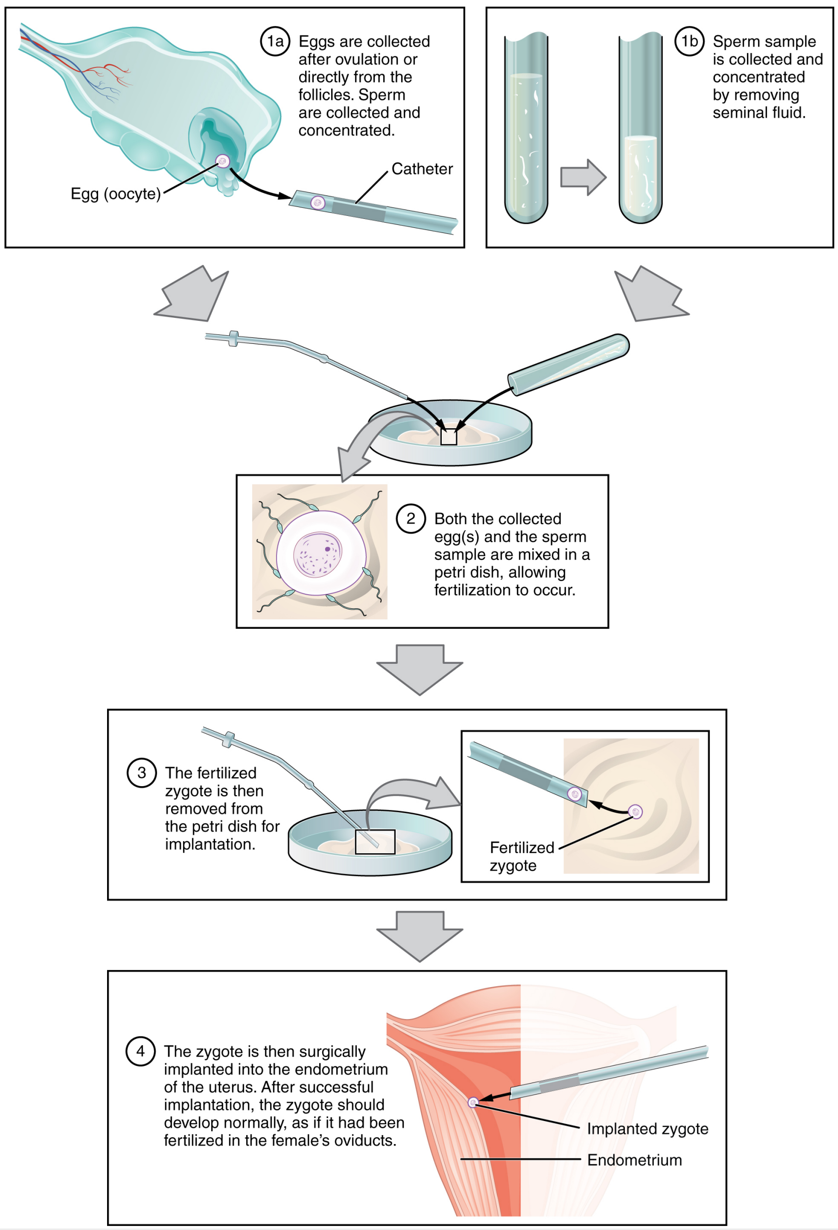
physician to visualize mature follicles. The ova are aspirated (sucked out) using a syringe.

In parallel, sperm are obtained from the male partner or from a sperm bank. The sperm are prepared by washing to remove seminal fluid because seminal fluid contains a peptide, FPP (or, fertilization promoting peptide), that—in high concentrations—prevents capacitation of the sperm. The sperm sample is also concentrated, to increase the sperm count per milliliter.

Next, the eggs and sperm are mixed in a petri dish. The ideal ratio is 75,000 sperm to one egg. If there are severe problems with the sperm—for example, the count is exceedingly low, or the sperm are completely nonmotile, or incapable of binding to or penetrating the zona pellucida—a sperm can be injected into an egg. This is called intracytoplasmic sperm injection (ICSI).

The embryos are then incubated until they either reach the eight-cell stage or the blastocyst stage. In the United States, fertilized eggs are typically cultured to the blastocyst stage because this results in a higher pregnancy rate. Finally, the embryos are transferred to a woman's uterus using a plastic catheter (tube). [link] illustrates the steps involved in IVF.

IVF



In vitro fertilization involves egg collection from the ovaries, fertilization in a petri dish, and the transfer of embryos into the uterus.

IVF is a relatively new and still evolving technology, and until recently it was necessary to transfer multiple embryos to achieve a good chance of a pregnancy. Today, however, transferred embryos are much more likely to implant successfully, so countries that regulate the IVF industry cap the

number of embryos that can be transferred per cycle at two. This reduces the risk of multiple-birth pregnancies.
The rate of success for IVF is correlated with a woman’s age. More than 40 percent of women under 35 succeed in giving birth following IVF, but the rate drops to a little over 10 percent in women over 40.

Note:

Go to this site to view resources covering various aspects of fertilization, including movies and animations showing sperm structure and motility, ovulation, and fertilization.

Chapter Review

Hundreds of millions of sperm deposited in the vagina travel toward the oocyte, but only a few hundred actually reach it. The number of sperm that reach the oocyte is greatly reduced because of conditions within the female reproductive tract. Many sperm are overcome by the acidity of the vagina, others are blocked by mucus in the cervix, whereas others are attacked by phagocytic leukocytes in the uterus. Those sperm that do survive undergo a change in response to those conditions. They go through the process of capacitation, which improves their motility and alters the membrane surrounding the acrosome, the cap-like structure in the head of a sperm that contains the digestive enzymes needed for it to attach to and penetrate the oocyte.

The oocyte that is released by ovulation is protected by a thick outer layer of granulosa cells known as the corona radiata and by the zona pellucida, a

thick glycoprotein membrane that lies just outside the oocyte’s plasma membrane. When capacitated sperm make contact with the oocyte, they release the digestive enzymes in the acrosome (the acrosomal reaction) and are thus able to attach to the oocyte and burrow through to the oocyte’s zona pellucida. One of the sperm will then break through to the oocyte’s plasma membrane and release its haploid nucleus into the oocyte. The oocyte’s membrane structure changes in response (cortical reaction), preventing any further penetration by another sperm and forming a fertilization membrane. Fertilization is complete upon unification of the haploid nuclei of the two gametes, producing a diploid zygote.

Review Questions

Exercise:

Problem: Sperm and ova are similar in terms of ________.

a. size
b. quantity produced per year
c. chromosome number
d. flagellar motility

Solution:

C

Exercise:

Problem:

Although the male ejaculate contains hundreds of millions of sperm, ________.

a. most do not reach the oocyte
b. most are destroyed by the alkaline environment of the uterus
c. it takes millions to penetrate the outer layers of the oocyte
d. most are destroyed by capacitation

Solution:

A

Exercise:

Problem:

As sperm first reach the oocyte, they will contact the ________.

a. acrosome
b. corona radiata
c. sperm-binding receptors
d. zona pellucida

Solution:

B

Exercise:

Problem: Fusion of pronuclei occurs during ________.

a. spermatogenesis
b. ovulation
c. fertilization
d. capacitation

Solution:

C

Exercise:

Problem:

Sperm must first complete ________ to enable the fertilization of an oocyte.

a. capacitation
b. the acrosomal reaction
c. the cortical reaction
d. the fast block

Solution:

A

Critical Thinking Questions

Exercise:

Problem:

Darcy and Raul are having difficulty conceiving a child. Darcy ovulates every 28 days, and Raul’s sperm count is normal. If we could observe Raul’s sperm about an hour after ejaculation, however, we’d see that they appear to be moving only sluggishly. When Raul’s sperm eventually encounter Darcy’s oocyte, they appear to be incapable of generating an adequate acrosomal reaction. Which process has probably gone wrong?

Solution:

The process of capacitation appears to be incomplete. Capacitation increases sperm motility and makes the sperm membrane more fragile. This enables it to release its digestive enzymes during the acrosomal reaction. When capacitation is inadequate, sperm cannot reach the oocyte membrane.

Exercise:

Problem:

Sherrise is a sexually active college student. On Saturday night, she has unprotected sex with her boyfriend. On Tuesday morning, she experiences the twinge of mid-cycle pain that she typically feels when she is ovulating. This makes Sherrise extremely anxious that she might soon learn she is pregnant. Is Sherrise's concern valid? Why or why not?

Solution:

Sherrise's concern is valid. Sperm may be viable for up to 4 days; therefore, it is entirely possible that capacitated sperm are still residing in her uterine tubes and could fertilize the oocyte she has just ovulated.

Glossary

acrosome
: cap-like vesicle located at the anterior-most region of a sperm that is rich with lysosomal enzymes capable of digesting the protective layers surrounding the oocyte

acrosomal reaction
: release of digestive enzymes by sperm that enables them to burrow through the corona radiata and penetrate the zona pellucida of an oocyte prior to fertilization

capacitation
: process that occurs in the female reproductive tract in which sperm are prepared for fertilization; leads to increased motility and changes in their outer membrane that improve their ability to release enzymes capable of digesting an oocyte's outer layers

corona radiata
: in an oocyte, a layer of granulosa cells that surrounds the oocyte and that must be penetrated by sperm before fertilization can occur

cortical reaction
following fertilization, the release of cortical granules from the oocyte’s plasma membrane into the zona pellucida creating a fertilization membrane that prevents any further attachment or penetration of sperm; part of the slow block to polyspermy

fertilization
unification of genetic material from male and female haploid gametes

fertilization membrane
impenetrable barrier that coats a nascent zygote; part of the slow block to polyspermy

polyspermy
penetration of an oocyte by more than one sperm

zona pellucida
thick, gel-like glycoprotein membrane that coats the oocyte and must be penetrated by sperm before fertilization can occur

zygote
fertilized egg; a diploid cell resulting from the fertilization of haploid gametes from the male and female lines

Embryonic Development
By the end of this section, you will be able to:

- Distinguish the stages of embryonic development that occur before implantation
- Describe the process of implantation
- List and describe four embryonic membranes
- Explain gastrulation
- Describe how the placenta is formed and identify its functions
- Explain how an embryo transforms from a flat disc of cells into a three-dimensional shape resembling a human
- Summarize the process of organogenesis

Throughout this chapter, we will express embryonic and fetal ages in terms of weeks from fertilization, commonly called conception. The period of time required for full development of a fetus in utero is referred to as **gestation** (gestare = “to carry” or “to bear”). It can be subdivided into distinct gestational periods. The first 2 weeks of prenatal development are referred to as the pre-embryonic stage. A developing human is referred to as an **embryo** during weeks 3–8, and a **fetus** from the ninth week of gestation until birth. In this section, we’ll cover the pre-embryonic and embryonic stages of development, which are characterized by cell division, migration, and differentiation. By the end of the embryonic period, all of the organ systems are structured in rudimentary form, although the organs themselves are either nonfunctional or only semi-functional.

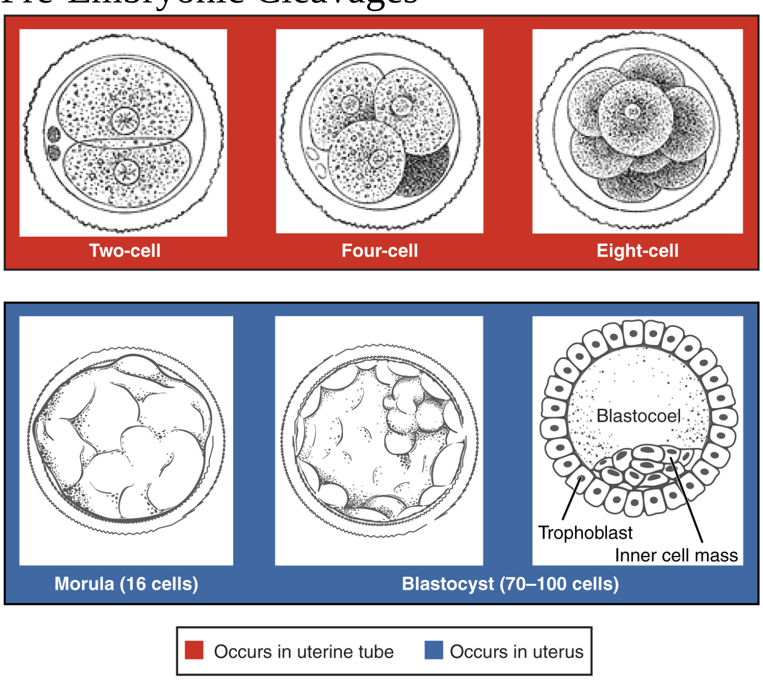
Pre-implantation Embryonic Development

Following fertilization, the zygote and its associated membranes, together referred to as the **conceptus**, continue to be projected toward the uterus by peristalsis and beating cilia. During its journey to the uterus, the zygote undergoes five or six rapid mitotic cell divisions. Although each **cleavage** results in more cells, it does not increase the total volume of the conceptus ([link]). Each daughter cell produced by cleavage is called a **blastomere** (blastos = “germ,” in the sense of a seed or sprout).

Approximately 3 days after fertilization, a 16-cell conceptus reaches the uterus. The cells that had been loosely grouped are now compacted and look more like a solid mass. The name given to this structure is the **morula** (morula = "little mulberry"). Once inside the uterus, the conceptus floats freely for several more days. It continues to divide, creating a ball of approximately 100 cells, and consuming nutritive endometrial secretions called uterine milk while the uterine lining thickens. The ball of now tightly bound cells starts to secrete fluid and organize themselves around a fluid-filled cavity, the **blastocoel**. At this developmental stage, the conceptus is referred to as a **blastocyst**. Within this structure, a group of cells forms into an **inner cell mass**, which is fated to become the embryo. The cells that form the outer shell are called **trophoblasts** (trophe = "to feed" or "to nourish"). These cells will develop into the chorionic sac and the fetal portion of the **placenta** (the organ of nutrient, waste, and gas exchange between mother and the developing offspring).

The inner mass of embryonic cells is totipotent during this stage, meaning that each cell has the potential to differentiate into any cell type in the human body. Totipotency lasts for only a few days before the cells' fates are set as being the precursors to a specific lineage of cells.

Pre-Embryonic Cleavages



Pre-embryonic cleavages make use of the

abundant cytoplasm of the conceptus as the cells rapidly divide without changing the total volume.

As the blastocyst forms, the trophoblast excretes enzymes that begin to degrade the zona pellucida. In a process called “hatching,” the conceptus breaks free of the zona pellucida in preparation for implantation.

Note:

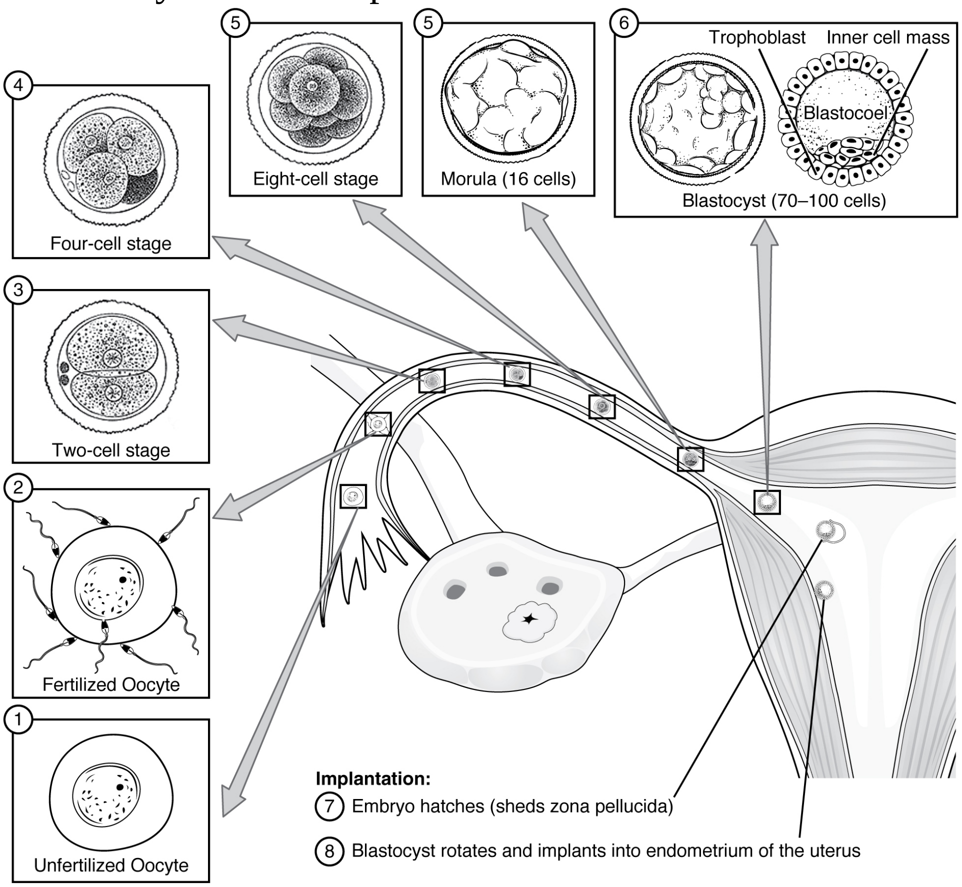
View this time-lapse movie of a conceptus starting at day 3. What is the first structure you see? At what point in the movie does the blastocoel first appear? What event occurs at the end of the movie?

Implantation

At the end of the first week, the blastocyst comes in contact with the uterine wall and adheres to it, embedding itself in the uterine lining via the trophoblast cells. Thus begins the process of **implantation**, which signals the end of the pre-embryonic stage of development ([link]). Implantation can be accompanied by minor bleeding. The blastocyst typically implants in the fundus of the uterus or on the posterior wall. However, if the endometrium is not fully developed and ready to receive the blastocyst, the blastocyst will detach and find a better spot. A significant percentage (50–75 percent) of blastocysts fail to implant; when this occurs, the blastocyst is shed with the endometrium during menses. The high rate of implantation

failure is one reason why pregnancy typically requires several ovulation cycles to achieve.

Pre-Embryonic Development

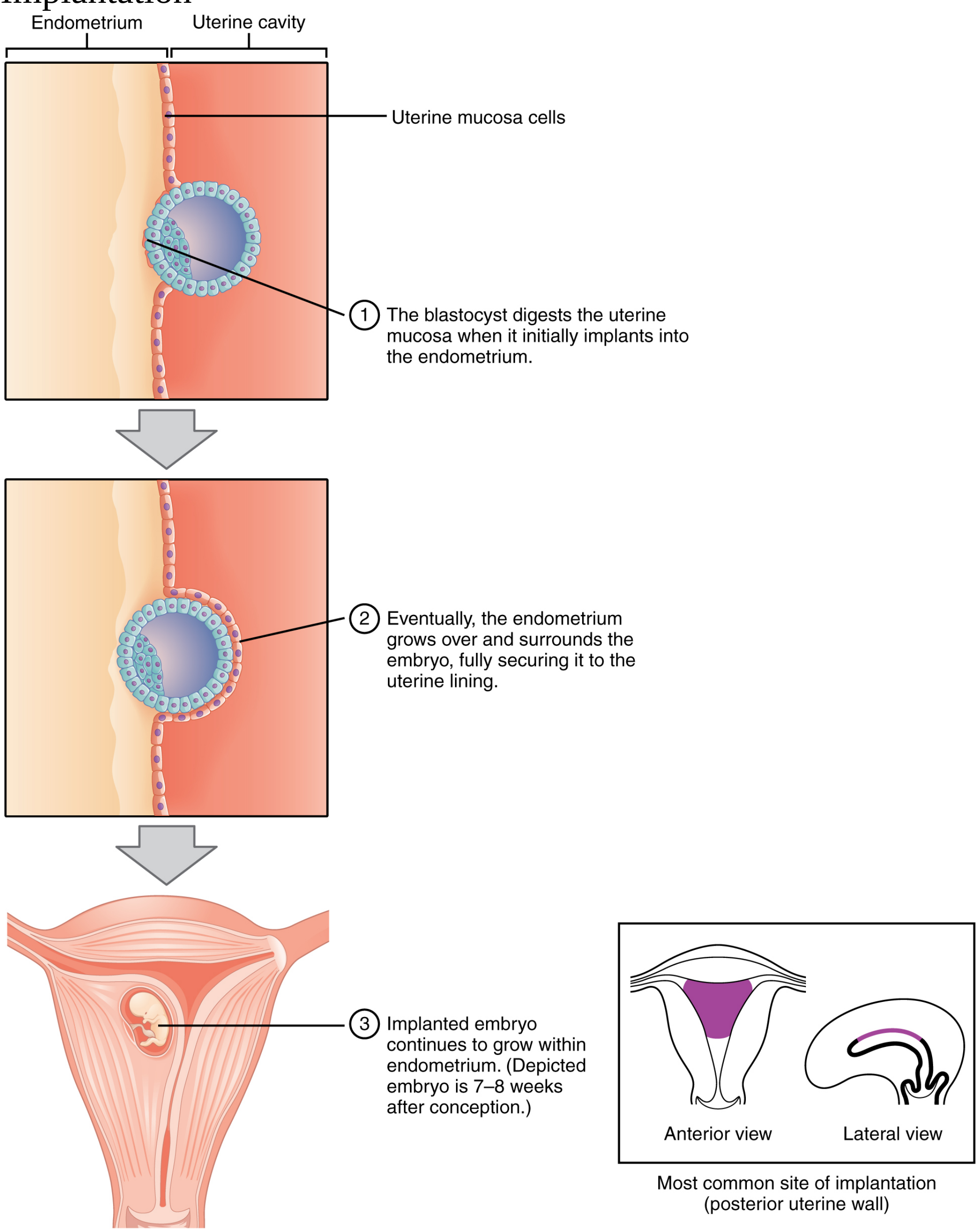


Ovulation, fertilization, pre-embryonic development, and implantation occur at specific locations within the female reproductive system in a time span of approximately 1 week.

When implantation succeeds and the blastocyst adheres to the endometrium, the superficial cells of the trophoblast fuse with each other, forming the **syncytiotrophoblast**, a multinucleated body that digests endometrial cells to firmly secure the blastocyst to the uterine wall. In response, the uterine mucosa rebuilds itself and envelops the blastocyst ([link]). The trophoblast secretes **human chorionic gonadotropin (hCG)**, a hormone that directs the corpus luteum to survive, enlarge, and continue

producing progesterone and estrogen to suppress menses. These functions of hCG are necessary for creating an environment suitable for the developing embryo. As a result of this increased production, hCG accumulates in the maternal bloodstream and is excreted in the urine. Implantation is complete by the middle of the second week. Just a few days after implantation, the trophoblast has secreted enough hCG for an at-home urine pregnancy test to give a positive result.

Implantation



During implantation, the trophoblast cells of the blastocyst adhere to the endometrium and digest endometrial cells until it is attached securely.

Most of the time an embryo implants within the body of the uterus in a location that can support growth and development. However, in one to two percent of cases, the embryo implants either outside the uterus (an **ectopic pregnancy**) or in a region of uterus that can create complications for the pregnancy. If the embryo implants in the inferior portion of the uterus, the placenta can potentially grow over the opening of the cervix, a condition call **placenta previa**.

Note:

Disorders of the…

Development of the Embryo

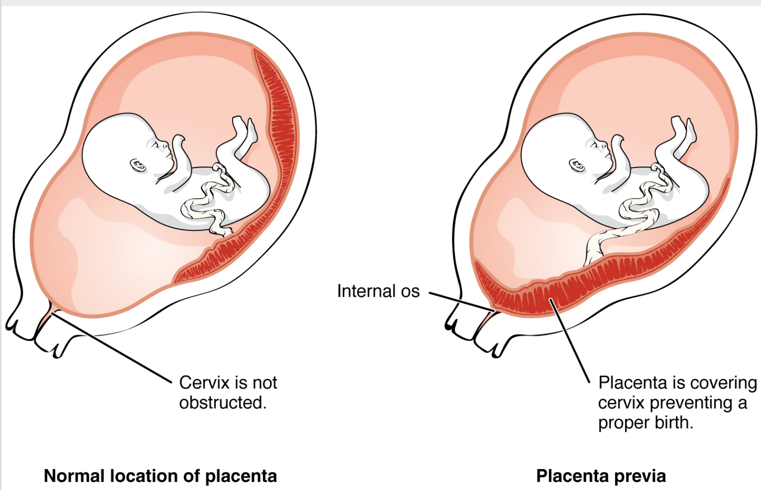
In the vast majority of ectopic pregnancies, the embryo does not complete its journey to the uterus and implants in the uterine tube, referred to as a tubal pregnancy. However, there are also ovarian ectopic pregnancies (in which the egg never left the ovary) and abdominal ectopic pregnancies (in which an egg was “lost” to the abdominal cavity during the transfer from ovary to uterine tube, or in which an embryo from a tubal pregnancy re-implanted in the abdomen). Once in the abdominal cavity, an embryo can implant into any well-vascularized structure—the rectouterine cavity (Douglas’ pouch), the mesentery of the intestines, and the greater omentum are some common sites.

Tubal pregnancies can be caused by scar tissue within the tube following a sexually transmitted bacterial infection. The scar tissue impedes the progress of the embryo into the uterus—in some cases “snagging” the embryo and, in other cases, blocking the tube completely. Approximately one half of tubal pregnancies resolve spontaneously. Implantation in a uterine tube causes bleeding, which appears to stimulate smooth muscle contractions and expulsion of the embryo. In the remaining cases, medical or surgical intervention is necessary. If an ectopic pregnancy is detected

early, the embryo’s development can be arrested by the administration of the cytotoxic drug methotrexate, which inhibits the metabolism of folic acid. If diagnosis is late and the uterine tube is already ruptured, surgical repair is essential.

Even if the embryo has successfully found its way to the uterus, it does not always implant in an optimal location (the fundus or the posterior wall of the uterus). Placenta previa can result if an embryo implants close to the internal os of the uterus (the internal opening of the cervix). As the fetus grows, the placenta can partially or completely cover the opening of the cervix ([link]). Although it occurs in only 0.5 percent of pregnancies, placenta previa is the leading cause of antepartum hemorrhage (profuse vaginal bleeding after week 24 of pregnancy but prior to childbirth).

Placenta Previa



An embryo that implants too close to the opening of the cervix can lead to placenta previa, a condition in which the placenta partially or completely covers the cervix.

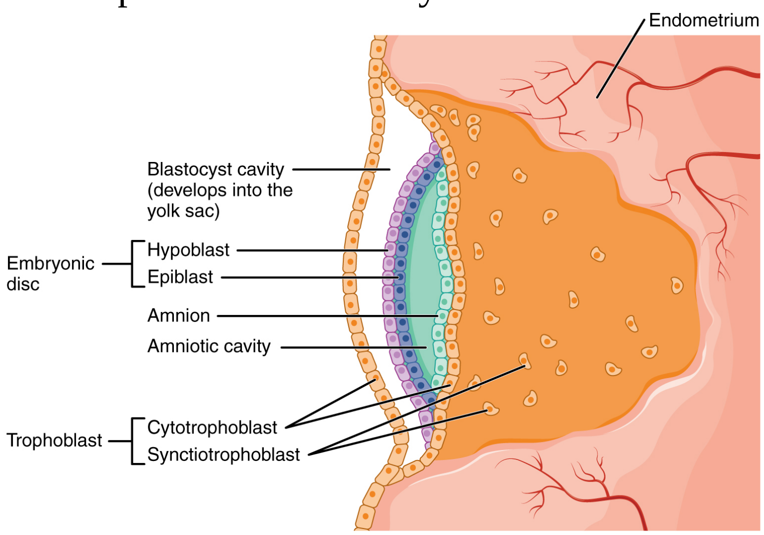
Embryonic Membranes

During the second week of development, with the embryo implanted in the uterus, cells within the blastocyst start to organize into layers. Some grow to

form the extra-embryonic membranes needed to support and protect the growing embryo: the amnion, the yolk sac, the allantois, and the chorion.

At the beginning of the second week, the cells of the inner cell mass form into a two-layered disc of embryonic cells, and a space—the **amniotic cavity**—opens up between it and the trophoblast ([link]). Cells from the upper layer of the disc (the **epiblast**) extend around the amniotic cavity, creating a membranous sac that forms into the **amnion** by the end of the second week. The amnion fills with amniotic fluid and eventually grows to surround the embryo. Early in development, amniotic fluid consists almost entirely of a filtrate of maternal plasma, but as the kidneys of the fetus begin to function at approximately the eighth week, they add urine to the volume of amniotic fluid. Floating within the amniotic fluid, the embryo—and later, the fetus—is protected from trauma and rapid temperature changes. It can move freely within the fluid and can prepare for swallowing and breathing out of the uterus.

Development of the Embryonic Disc



Formation of the embryonic disc leaves spaces on either side that develop into the amniotic cavity and the yolk sac.

On the ventral side of the embryonic disc, opposite the amnion, cells in the lower layer of the embryonic disk (the **hypoblast**) extend into the blastocyst

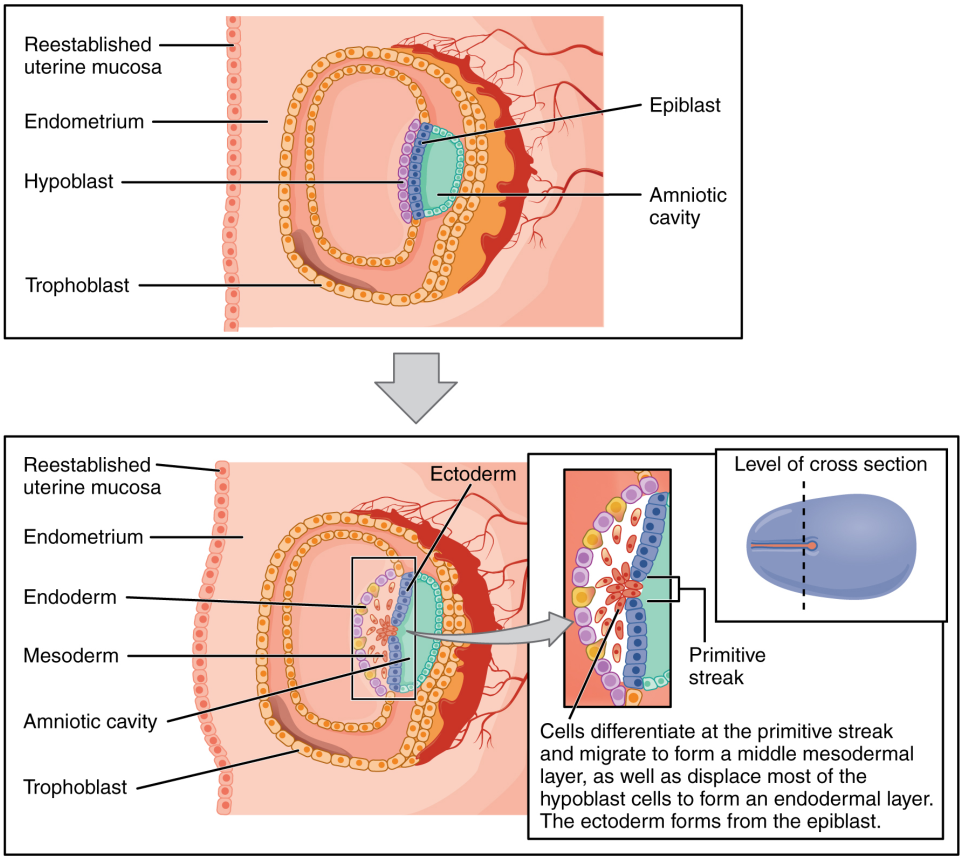
cavity and form a **yolk sac**. The yolk sac supplies some nutrients absorbed from the trophoblast and also provides primitive blood circulation to the developing embryo for the second and third week of development. When the placenta takes over nourishing the embryo at approximately week 4, the yolk sac has been greatly reduced in size and its main function is to serve as the source of blood cells and germ cells (cells that will give rise to gametes). During week 3, a finger-like outpocketing of the yolk sac develops into the **allantois**, a primitive excretory duct of the embryo that will become part of the urinary bladder. Together, the stalks of the yolk sac and allantois establish the outer structure of the umbilical cord.

The last of the extra-embryonic membranes is the **chorion**, which is the one membrane that surrounds all others. The development of the chorion will be discussed in more detail shortly, as it relates to the growth and development of the placenta.

Embryogenesis

As the third week of development begins, the two-layered disc of cells becomes a three-layered disc through the process of **gastrulation**, during which the cells transition from totipotency to multipotency. The embryo, which takes the shape of an oval-shaped disc, forms an indentation called the **primitive streak** along the dorsal surface of the epiblast. A node at the caudal or “tail” end of the primitive streak emits growth factors that direct cells to multiply and migrate. Cells migrate toward and through the primitive streak and then move laterally to create two new layers of cells. The first layer is the **endoderm**, a sheet of cells that displaces the hypoblast and lies adjacent to the yolk sac. The second layer of cells fills in as the middle layer, or **mesoderm**. The cells of the epiblast that remain (not having migrated through the primitive streak) become the **ectoderm** ([link]).

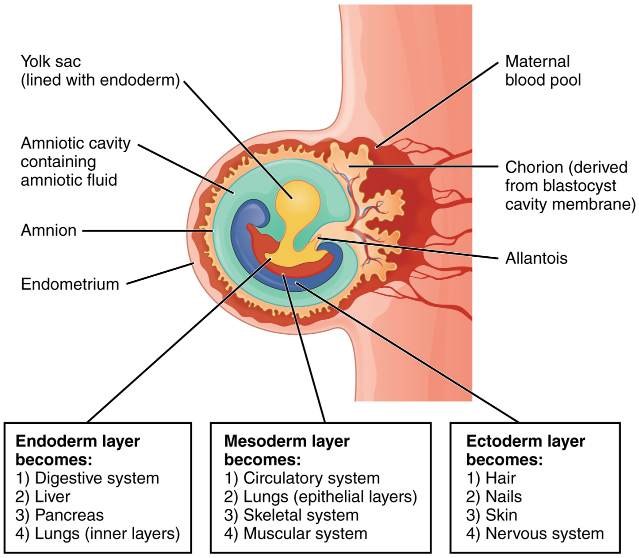
Germ Layers



Formation of the three primary germ layers occurs during the first 2 weeks of development. The embryo at this stage is only a few millimeters in length.

Each of these germ layers will develop into specific structures in the embryo. Whereas the ectoderm and endoderm form tightly connected epithelial sheets, the mesodermal cells are less organized and exist as a loosely connected cell community. The ectoderm gives rise to cell lineages that differentiate to become the central and peripheral nervous systems, sensory organs, epidermis, hair, and nails. Mesodermal cells ultimately become the skeleton, muscles, connective tissue, heart, blood vessels, and kidneys. The endoderm goes on to form the epithelial lining of the gastrointestinal tract, liver, and pancreas, as well as the lungs ([link]).

Fates of Germ Layers in Embryo



Following gastrulation of the embryo in the third week, embryonic cells of the ectoderm, mesoderm, and endoderm begin to migrate and differentiate into the cell lineages that will give rise to mature organs and organ systems in the infant.

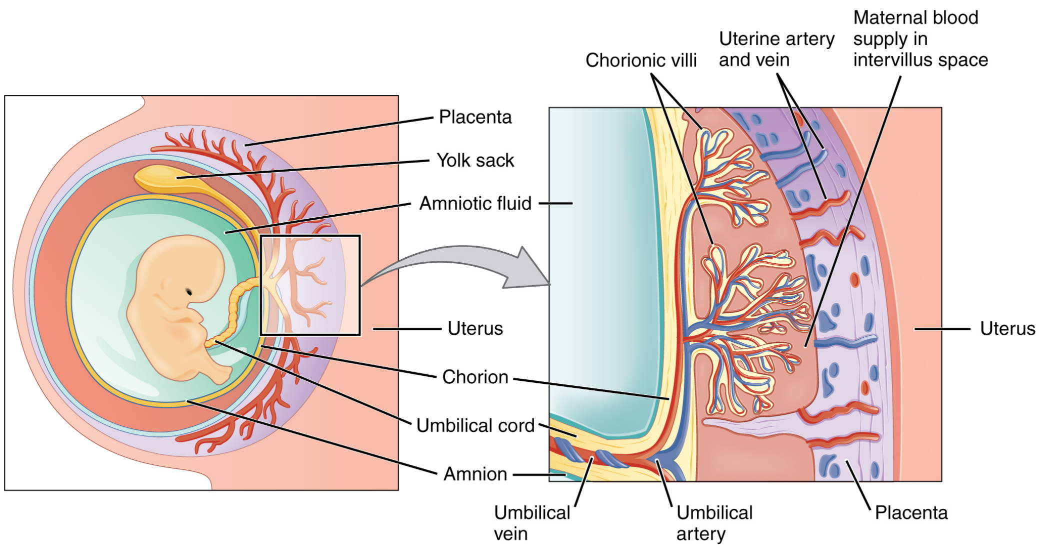
Development of the Placenta

During the first several weeks of development, the cells of the endometrium—referred to as decidual cells—nourish the nascent embryo. During prenatal weeks 4–12, the developing placenta gradually takes over the role of feeding the embryo, and the decidual cells are no longer needed. The mature placenta is composed of tissues derived from the embryo, as well as maternal tissues of the endometrium. The placenta connects to the conceptus via the **umbilical cord**, which carries deoxygenated blood and wastes from the fetus through two umbilical arteries; nutrients and oxygen are carried from the mother to the fetus through the single umbilical vein. The umbilical cord is surrounded by the amnion, and the spaces within the

cord around the blood vessels are filled with Wharton’s jelly, a mucous connective tissue.

The maternal portion of the placenta develops from the deepest layer of the endometrium, the decidua basalis. To form the embryonic portion of the placenta, the syncytiotrophoblast and the underlying cells of the trophoblast (cytotrophoblast cells) begin to proliferate along with a layer of extraembryonic mesoderm cells. These form the **chorionic membrane**, which envelops the entire conceptus as the chorion. The chorionic membrane forms finger-like structures called **chorionic villi** that burrow into the endometrium like tree roots, making up the fetal portion of the placenta. The cytotrophoblast cells perforate the chorionic villi, burrow farther into the endometrium, and remodel maternal blood vessels to augment maternal blood flow surrounding the villi. Meanwhile, fetal mesenchymal cells derived from the mesoderm fill the villi and differentiate into blood vessels, including the three umbilical blood vessels that connect the embryo to the developing placenta ([link]).

Cross-Section of the Placenta



In the placenta, maternal and fetal blood components are conducted through the surface of the chorionic villi, but maternal and fetal bloodstreams never mix directly.

The placenta develops throughout the embryonic period and during the first several weeks of the fetal period; **placentation** is complete by weeks 14–16. As a fully developed organ, the placenta provides nutrition and excretion, respiration, and endocrine function ([link] and [link]). It receives blood from the fetus through the umbilical arteries. Capillaries in the chorionic villi filter fetal wastes out of the blood and return clean, oxygenated blood to the fetus through the umbilical vein. Nutrients and oxygen are transferred from maternal blood surrounding the villi through the capillaries and into the fetal bloodstream. Some substances move across the placenta by simple diffusion. Oxygen, carbon dioxide, and any other lipid-soluble substances take this route. Other substances move across by facilitated diffusion. This includes water-soluble glucose. The fetus has a high demand for amino acids and iron, and those substances are moved across the placenta by active transport.

Maternal and fetal blood does not commingle because blood cells cannot move across the placenta. This separation prevents the mother's cytotoxic T cells from reaching and subsequently destroying the fetus, which bears "non-self" antigens. Further, it ensures the fetal red blood cells do not enter the mother's circulation and trigger antibody development (if they carry "non-self" antigens)—at least until the final stages of pregnancy or birth. This is the reason that, even in the absence of preventive treatment, an Rh^- mother doesn't develop antibodies that could cause hemolytic disease in her first Rh^+ fetus.

Although blood cells are not exchanged, the chorionic villi provide ample surface area for the two-way exchange of substances between maternal and fetal blood. The rate of exchange increases throughout gestation as the villi become thinner and increasingly branched. The placenta is permeable to lipid-soluble fetotoxic substances: alcohol, nicotine, barbiturates, antibiotics, certain pathogens, and many other substances that can be dangerous or fatal to the developing embryo or fetus. For these reasons, pregnant women should avoid fetotoxic substances. Alcohol consumption by pregnant women, for example, can result in a range of abnormalities referred to as fetal alcohol spectrum disorders (FASD). These include organ and facial malformations, as well as cognitive and behavioral disorders.

Functions of the Placenta		
Nutrition and digestion	**Respiration**	**Endocrine function**
• Mediates diffusion of maternal glucose, amino acids, fatty acids, vitamins, and minerals • Stores nutrients during early pregnancy to accommodate increased fetal demand later in pregnancy • Excretes and filters fetal nitrogenous wastes into maternal blood	• Mediates maternal-to-fetal oxygen transport and fetal-to-maternal carbon dioxide transport	• Secretes several hormones, including hCG, estrogens, and progesterone, to maintain the pregnancy and stimulate maternal and fetal development • Mediates the transmission of maternal hormones into fetal blood and vice versa

Placenta

This post-expulsion placenta and umbilical cord (white) are viewed from the fetal side.

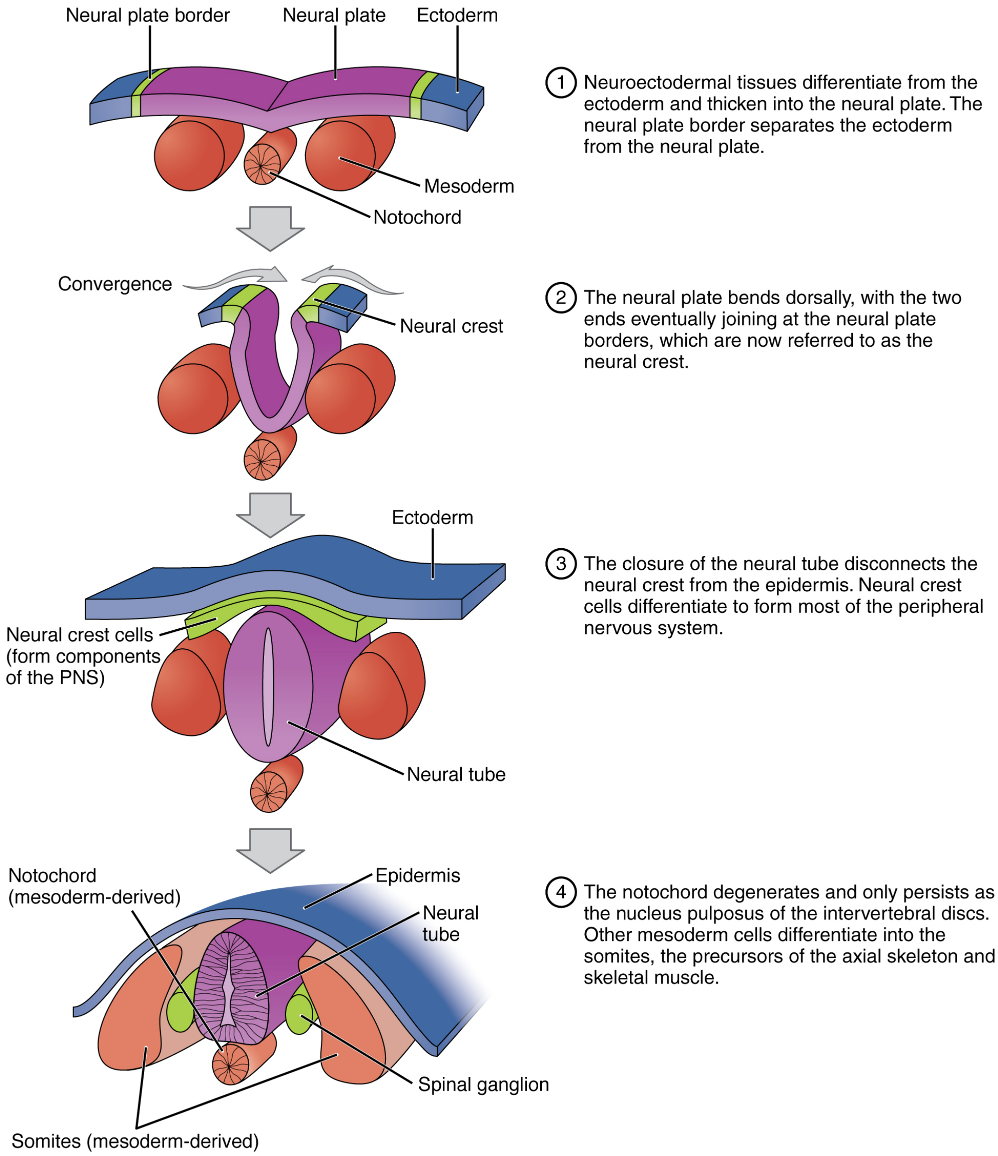
Organogenesis

Following gastrulation, rudiments of the central nervous system develop from the ectoderm in the process of **neurulation** ([link]). Specialized neuroectodermal tissues along the length of the embryo thicken into the **neural plate**. During the fourth week, tissues on either side of the plate fold upward into a **neural fold**. The two folds converge to form the **neural tube**. The tube lies atop a rod-shaped, mesoderm-derived **notochord**, which eventually becomes the nucleus pulposus of intervertebral discs. Block-like structures called **somites** form on either side of the tube, eventually differentiating into the axial skeleton, skeletal muscle, and dermis. During the fourth and fifth weeks, the anterior neural tube dilates and subdivides to form vesicles that will become the brain structures.

Folate, one of the B vitamins, is important to the healthy development of the neural tube. A deficiency of maternal folate in the first weeks of pregnancy can result in neural tube defects, including spina bifida—a birth defect in which spinal tissue protrudes through the newborn’s vertebral

column, which has failed to completely close. A more severe neural tube defect is anencephaly, a partial or complete absence of brain tissue.

Neurulation

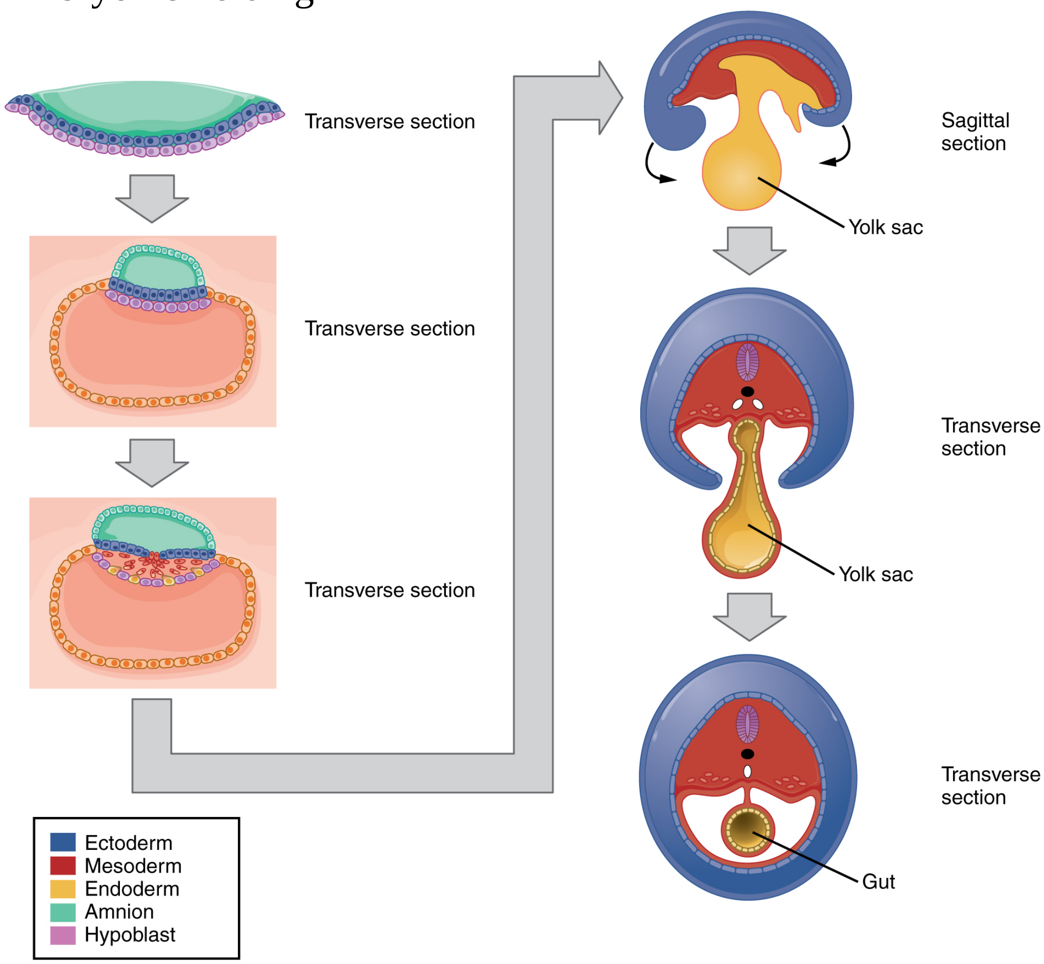


The embryonic process of neurulation establishes the rudiments of the future central nervous system and skeleton.

The embryo, which begins as a flat sheet of cells, begins to acquire a cylindrical shape through the process of **embryonic folding** ([link]). The

embryo folds laterally and again at either end, forming a C-shape with distinct head and tail ends. The embryo envelops a portion of the yolk sac, which protrudes with the umbilical cord from what will become the abdomen. The folding essentially creates a tube, called the primitive gut, that is lined by the endoderm. The amniotic sac, which was sitting on top of the flat embryo, envelops the embryo as it folds.

Embryonic Folding



Embryonic folding converts a flat sheet of cells into a hollow, tube-like structure.

Within the first 8 weeks of gestation, a developing embryo establishes the rudimentary structures of all of its organs and tissues from the ectoderm, mesoderm, and endoderm. This process is called **organogenesis**.

Like the central nervous system, the heart also begins its development in the embryo as a tube-like structure, connected via capillaries to the chorionic villi. Cells of the primitive tube-shaped heart are capable of electrical conduction and contraction. The heart begins beating in the beginning of the fourth week, although it does not actually pump embryonic blood until a week later, when the oversized liver has begun producing red blood cells. (This is a temporary responsibility of the embryonic liver that the bone marrow will assume during fetal development.) During weeks 4–5, the eye pits form, limb buds become apparent, and the rudiments of the pulmonary system are formed.

During the sixth week, uncontrolled fetal limb movements begin to occur. The gastrointestinal system develops too rapidly for the embryonic abdomen to accommodate it, and the intestines temporarily loop into the umbilical cord. Paddle-shaped hands and feet develop fingers and toes by the process of apoptosis (programmed cell death), which causes the tissues between the fingers to disintegrate. By week 7, the facial structure is more complex and includes nostrils, outer ears, and lenses ([link]). By the eighth week, the head is nearly as large as the rest of the embryo's body, and all major brain structures are in place. The external genitalia are apparent, but at this point, male and female embryos are indistinguishable. Bone begins to replace cartilage in the embryonic skeleton through the process of ossification. By the end of the embryonic period, the embryo is approximately 3 cm (1.2 in) from crown to rump and weighs approximately 8 g (0.25 oz).

Embryo at 7 Weeks

An embryo at the end of 7 weeks of development is only 10 mm in length, but its developing eyes, limb buds, and tail are already visible. (This embryo was derived from an ectopic pregnancy.) (credit: Ed Uthman)

Note:

Use this interactive tool to view the process of embryogenesis from fertilization through pregnancy to birth. Can you identify when neurulation occurs in the embryo?

Chapter Review

As the zygote travels toward the uterus, it undergoes numerous cleavages in which the number of cells doubles (blastomeres). Upon reaching the uterus, the conceptus has become a tightly packed sphere of cells called the morula, which then forms into a blastocyst consisting of an inner cell mass within a fluid-filled cavity surrounded by trophoblasts. The blastocyst implants in the uterine wall, the trophoblasts fuse to form a syncytiotrophoblast, and the conceptus is enveloped by the endometrium. Four embryonic membranes form to support the growing embryo: the amnion, the yolk sac, the allantois, and the chorion. The chorionic villi of the chorion extend into the endometrium to form the fetal portion of the placenta. The placenta supplies the growing embryo with oxygen and nutrients; it also removes carbon dioxide and other metabolic wastes.

Following implantation, embryonic cells undergo gastrulation, in which they differentiate and separate into an embryonic disc and establish three primary germ layers (the endoderm, mesoderm, and ectoderm). Through the process of embryonic folding, the fetus begins to take shape. Neurulation starts the process of the development of structures of the central nervous system and organogenesis establishes the basic plan for all organ systems.

Interactive Link Questions

Exercise:

Problem:

View this time-lapse movie of a conceptus starting at day 3. What is the first structure you see? At what point in the movie does the blastocoel first appear? What event occurs at the end of the movie?

Solution:

The first structure shown is the morula. The blastocoel appears at approximately 20 seconds. The movie ends with the hatching of the conceptus.

Review Questions

Exercise:

Problem: Cleavage produces daughter cells called ________.

a. trophoblasts
b. blastocysts
c. morulae
d. blastomeres

Solution:

D

Exercise:

Problem: The conceptus, upon reaching the uterus, first ________.

a. implants
b. divides
c. disintegrates
d. hatches

Solution:

B

Exercise:

Problem:

The inner cell mass of the blastocyst is destined to become the ________.

a. embryo
b. trophoblast
c. chorionic villi
d. placenta

Solution:

A

Exercise:

Problem:

Which primary germ layer gave rise to the cells that eventually became the central nervous system?

a. endoderm
b. ectoderm
c. acrosome
d. mesoderm

Solution:

B

Exercise:

Problem:

What would happen if the trophoblast did not secrete hCG upon implantation of the blastocyst?

a. The cells would not continue to divide.

b. The corpus luteum would continue to produce progesterone and estrogen.
c. Menses would flush the blastocyst out of the uterus.
d. The uterine mucosa would not envelop the blastocyst.

Solution:

C

Exercise:

Problem: During what process does the amnion envelop the embryo?

a. embryonic folding
b. gastrulation
c. implantation
d. organogenesis

Solution:

A

Exercise:

Problem: The placenta is formed from ________.

a. the embryo’s mesenchymal cells
b. the mother’s endometrium only
c. the mother’s endometrium and the embryo’s chorionic membrane
d. the mother’s endometrium and the embryo’s umbilical cord

Solution:

C

Critical Thinking Questions

Exercise:

Problem:

Approximately 3 weeks after her last menstrual period, a sexually active woman experiences a brief episode of abdominopelvic cramping and minor bleeding. What might be the explanation?

Solution:

The timing of this discomfort and bleeding suggests that it is probably caused by implantation of the blastocyst into the uterine wall.

Exercise:

Problem:

The Food and Nutrition Board of the Institute of Medicine recommends that all women who might become pregnant consume at least 400 μg/day of folate from supplements or fortified foods. Why?

Solution:

Folate, one of the B vitamins, is important for the healthy formation of the embryonic neural tube, which occurs in the first few weeks following conception—often before a woman even realizes she is pregnant. A folate-deficient environment increases the risk of a neural tube defect, such as spina bidifa, in the newborn.

Glossary

allantois
: finger-like outpocketing of yolk sac forms the primitive excretory duct of the embryo; precursor to the urinary bladder

amnion

transparent membranous sac that encloses the developing fetus and fills with amniotic fluid

amniotic cavity
cavity that opens up between the inner cell mass and the trophoblast; develops into amnion

blastocoel
fluid-filled cavity of the blastocyst

blastocyst
term for the conceptus at the developmental stage that consists of about 100 cells shaped into an inner cell mass that is fated to become the embryo and an outer trophoblast that is fated to become the associated fetal membranes and placenta

blastomere
daughter cell of a cleavage

chorion
membrane that develops from the syncytiotrophoblast, cytotrophoblast, and mesoderm; surrounds the embryo and forms the fetal portion of the placenta through the chorionic villi

chorionic membrane
precursor to the chorion; forms from extra-embryonic mesoderm cells

chorionic villi
projections of the chorionic membrane that burrow into the endometrium and develop into the placenta

cleavage
form of mitotic cell division in which the cell divides but the total volume remains unchanged; this process serves to produce smaller and smaller cells

conceptus
pre-implantation stage of a fertilized egg and its associated membranes

ectoderm
: primary germ layer that develops into the central and peripheral nervous systems, sensory organs, epidermis, hair, and nails

ectopic pregnancy
: implantation of an embryo outside of the uterus

embryo
: developing human during weeks 3–8

embryonic folding
: process by which an embryo develops from a flat disc of cells to a three-dimensional shape resembling a cylinder

endoderm
: primary germ layer that goes on to form the gastrointestinal tract, liver, pancreas, and lungs

epiblast
: upper layer of cells of the embryonic disc that forms from the inner cell mass; gives rise to all three germ layers

fetus
: developing human during the time from the end of the embryonic period (week 9) to birth

gastrulation
: process of cell migration and differentiation into three primary germ layers following cleavage and implantation

gestation
: in human development, the period required for embryonic and fetal development in utero; pregnancy

human chorionic gonadotropin (hCG)
: hormone that directs the corpus luteum to survive, enlarge, and continue producing progesterone and estrogen to suppress menses and secure an environment suitable for the developing embryo

hypoblast
: lower layer of cells of the embryonic disc that extend into the blastocoel to form the yolk sac

implantation
: process by which a blastocyst embeds itself in the uterine endometrium

inner cell mass
: cluster of cells within the blastocyst that is fated to become the embryo

mesoderm
: primary germ layer that becomes the skeleton, muscles, connective tissue, heart, blood vessels, and kidneys

morula
: tightly packed sphere of blastomeres that has reached the uterus but has not yet implanted itself

neural plate
: thickened layer of neuroepithelium that runs longitudinally along the dorsal surface of an embryo and gives rise to nervous system tissue

neural fold
: elevated edge of the neural groove

neural tube
: precursor to structures of the central nervous system, formed by the invagination and separation of neuroepithelium

neurulation
: embryonic process that establishes the central nervous system

notochord
: rod-shaped, mesoderm-derived structure that provides support for growing fetus

organogenesis

development of the rudimentary structures of all of an embryo’s organs from the germ layers

placenta
: organ that forms during pregnancy to nourish the developing fetus; also regulates waste and gas exchange between mother and fetus

placenta previa
: low placement of fetus within uterus causes placenta to partially or completely cover the opening of the cervix as it grows

placentation
: formation of the placenta; complete by weeks 14–16 of pregnancy

primitive streak
: indentation along the dorsal surface of the epiblast through which cells migrate to form the endoderm and mesoderm during gastrulation

somite
: one of the paired, repeating blocks of tissue located on either side of the notochord in the early embryo

syncytiotrophoblast
: superficial cells of the trophoblast that fuse to form a multinucleated body that digests endometrial cells to firmly secure the blastocyst to the uterine wall

trophoblast
: fluid-filled shell of squamous cells destined to become the chorionic villi, placenta, and associated fetal membranes

umbilical cord
: connection between the developing conceptus and the placenta; carries deoxygenated blood and wastes from the fetus and returns nutrients and oxygen from the mother

yolk sac

membrane associated with primitive circulation to the developing embryo; source of the first blood cells and germ cells and contributes to the umbilical cord structure